Malaysian Pharmacovigilance Guidelines

First Edition 2002

Adapted from the:

2. EMA Guideline on Good Pharmacovigilance Practices (GVP) – Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) – June 2013
5. ICH E2E Guideline: Pharmacovigilance planning – November 2004
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PREAMBLE

This guidance document has been developed to outline the requirements and procedures for submission of adverse drug reaction (ADR) reports and information regarding product safety to the Drug Control Authority (DCA).

The Drug Control Authority (DCA) established under the Control of Drugs and Cosmetics Regulations 1984 is tasked to ensure the safety, quality and efficacy of medicinal products registered in Malaysia.

Under the current arrangement, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) acts as the advisory body to DCA on local and international drug safety issues. The National Adverse Drug Reaction Monitoring Centre, located within the National Pharmaceutical Regulatory Agency (NPRA) serves as the secretariat to MADRAC, and has been a member of the World Health Organisation (WHO) Programme for International Drug Safety Monitoring since 1990.

Although this guidance document and certain stipulations are not obligatory, product registration holders (PRHs) and healthcare professionals are encouraged to comply in the spirit of cooperation towards ensuring the safety profile of medicinal products registered in Malaysia.

The recommendations in this guidance document will help to improve the quality and standard of product safety monitoring in Malaysia.
ACKNOWLEDGEMENTS

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GLOSSARY

Abuse of a medicinal product
Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

Adverse event (AE); synonym: Adverse experience
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse event following immunisation (AEFI)
Any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

A separate guideline for healthcare providers entitled Garispanduan Farmakovigilans Vaksin untuk Anggota Kesihatan is available for further information. Any details pertaining adverse event following immunisation (AEFI), Garispanduan Farmakovigilans Vaksin untuk Anggota Kesihatan should be used as an ultimate reference.

Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect
A response which is noxious or unintended to a medicinal product that is administered in standard doses by the proper route for the purpose of prophylaxis, diagnosis, or treatment.

The response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the registered indication or from occupational exposure. Conditions of use outside the registered indication include off-label use, overdose, misuse, abuse and medication errors.

Authority
Drug Control Authority/Pihak Berkuasa Kawalan Dadah

Clinical trial
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one country.

Closed signal
In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval.
Company core data sheet (CCDS)
For medicinal products, a document prepared by the product registration holder containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.

Company core safety information (CCSI)
For medicinal products, all relevant safety information contained in the company core data sheet prepared by the product registration holder and which product registration holder requires to be listed in all countries where the company markets the product, except when the regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purposes of periodic reporting for medicinal products, but not by which expected and unexpected are determined for expedited reporting.

Compassionate use of a medicinal product
Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by registered medicinal product.

Completed clinical trial
Study for which a final clinical study report is available.

Consumer
For the purpose of reporting cases of suspected adverse reactions, a person who is not a healthcare professional.

Consumer medication information leaflet/Risalah makanmat ubat untuk pengguna (RiMUP)
A leaflet containing information for the consumer on how to use the medicinal product safely and effectively.

Data lock point
For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date or the date of registration approval.

Direct healthcare professional communication (DHPC)
A communication intervention by which important information is delivered directly to individual healthcare professionals by a product registration holder or by a medicines authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals.

Generic medicinal product
A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the innovator medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Healthcare professional
For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and other allied healthcare professionals.

Identified risk
An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.
Important identified risk and important potential risk
An identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health.

Important potential risk
See Important identified risk and Important potential risk.

International birth date (IBD)
The date of the first registration/marketing authorisation for any product containing the active substance granted to any company in any country in the world.

Medicinal product
A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose;

or

A drug to be used as an ingredient of a preparation for a medicinal purpose.

Minimum criteria for reporting
For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are: an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicinal product.

Missing information
Gaps in knowledge, related to safety or particular patient populations, which could be clinically significant.

Misuse of a medicinal product
Situations where the medicinal product is intentionally and inappropriately used not in accordance with the registered information.

Newly identified signal
In periodic benefit-risk evaluation reports, a signal first identified during the reporting interval, prompting further actions or evaluation. This definition could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation.

Non-interventional studies
Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort and other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as normal clinical practice.

Off-label use
Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the registered indication or information.

Ongoing clinical trial
Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available.
Ongoing signal
In periodic benefit-risk evaluation reports, a signal that remains under evaluation at the data lock point. See also Signal, Data lock point.

Overdose
Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose. Clinical judgement should always be applied.

Package insert
An insert containing information for the user which accompanies the medicinal product.

Periodic benefit-risk evaluation report (PBRER)
Format and content for providing an evaluation of the benefit-risk balance of a medicinal product for submission by the product registration holder at defined time points after the approval of registration.

Pharmacovigilance
Science and activities relating to the detection, assessment, understanding and prevention of medicine-related problem.

Pharmacovigilance system
A system used by the product registration holder to fulfil the pharmacovigilance tasks and responsibilities listed in national regulations and designed to monitor the safety of registered medicinal products and detect any change to their benefit-risk balance.

In general, a pharmacovigilance system is a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their benefit-risk balance.

Potential risk
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.

Reference safety information
In periodic benefit-risk evaluation reports for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the product registration holder.

It is a subset of information contained within the product registration holder’s reference product information for the periodic benefit-risk evaluation report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information.

Registry
An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Risk management plan (RMP)
A detailed description of the risk management system.

Risk management system
A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.
Risk minimisation activity; synonym: Risk minimisation measure
An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur.

These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimisation activities (e.g. healthcare professional or patient communications/educational materials).

Risks related to use of a medicinal product
Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.

Safety concern
An important identified risk, important potential risk or missing information.

Serious adverse reaction
An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Signal
Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Signal management process
Includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action.

It therefore is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks causally associated with an active substance or a medicinal product or whether known risks have changed.

Signal validation
Process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.
Solicited sources of individual case safety reports
Organised data collection systems, which include clinical trials, registries, post-authorisation named-patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare professionals or information gathering on efficacy or patient compliance.

Spontaneous report, synonym: Spontaneous notification
An unsolicited communication by a healthcare professional or consumer to a product registration holder or the Authority.

Target population (treatment)
The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information.

Unexpected adverse reaction
An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

Validated signal
A signal where the signal validation process of evaluating the data supporting the detected signal has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.
### ABBREVIATIONS

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<th>Description</th>
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<tbody>
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<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
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<td>CCDS</td>
<td>Company Core Data Sheet</td>
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<tr>
<td>CIOMS</td>
<td>Council for International Organisation of Medical Sciences</td>
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<td>DCA</td>
<td>Drug Control Authority</td>
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<td>DHPC</td>
<td>Direct Healthcare Professional Communication</td>
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<tr>
<td>DLP</td>
<td>Data Lock Point</td>
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<tr>
<td>IBD</td>
<td>International Birth Date</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonisation</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Drug Regulatory Agency</td>
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<td>NPRA</td>
<td>National Pharmaceutical Regulatory Agency</td>
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<td>OTC</td>
<td>Over-the-counter</td>
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<td>PBRER</td>
<td>Periodic Benefit-Risk Evaluation Report</td>
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<td>PRH</td>
<td>Product Registration Holder</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>PV</td>
<td>Pharmacovigilance</td>
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<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SNOMED-CT</td>
<td>Systematised Nomenclature of Medicine – Clinical Term</td>
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<tr>
<td>SOC</td>
<td>System Organ Class</td>
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<tr>
<td>WHO</td>
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PART 1

INTRODUCTION TO PHARMACOVIGILANCE
PART 1: INTRODUCTION TO PHARMACOVIGILANCE

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 hospitals 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 used the medicinal product.

P1.1 BASIC PRINCIPLE OF PHARMACOVIGILANCE

P1.1.1 Definition of Pharmacovigilance

i. Pharmacovigilance is defined by the World Health Organisation (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

ii. In line with this definition, the objectives of pharmacovigilance are:-

   a) To identify previously unrecognised adverse reactions or changes in the patterns of adverse effects;
   b) To prevent harm from adverse reactions arising from the use of medicinal products;
   c) To assess the risks and benefits of products in order to determine what actions, if any, are necessary to improve their safe use;
   d) To promote the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public as well as to monitor the impact of any action taken.

P1.2 ADVERSE DRUG REACTION REPORTING

i. Reporting of adverse drug reactions (ADRs) is the main activity in pharmacovigilance, to improve the safety profile of medicinal products. The National ADR Monitoring Centre, National Pharmaceutical Regulatory Agency (NPRA) is committed to this scheme in order to ensure the safe use of medicinal products throughout the country.

ii. Information from the spontaneous ADR reporting schemes, in combination with clinical and epidemiological studies as well as literature, are used to aid decision-making on product safety. Information from all these sources may lead to the following regulatory changes:-

   - Withdrawal of the active ingredient(s) and/or product(s) from the market when the risk is considered unacceptable;
   - Revocation of the manufacturing license;
   - Restriction in usage;
   - Refinement of dosage instructions;
• Strengthening of specific warnings;
• Reviewing of specific labelling requirements;
• Changes in product information based on the new findings.

P1.3 LEGAL BASIS

i. In accordance with ‘Regulation 28: Reporting adverse reaction’ under the Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment 2006), product registration holders or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction arising from the use of the registered product.

ii. All product registration holders (PRHs) must ensure that a pharmacovigilance system is in place by the company and appropriate action is taken, when necessary.

iii. PRHs are required to monitor and report any product safety issues that arise locally or internationally to the NPRA as well as comply with all safety-related directives issued by the Authority.

iv. If PRHs fail to inform the Authority of any serious adverse reactions within the timeline stipulated in this guidance document, the registration status of the product(s) involved may be affected.

P1.4 CONFIDENTIALITY

The Authority will maintain strict confidentiality with regards to the identity of patients and reporters. Reporters are not required to disclose the identity of patients in reports.

P1.5 SCOPE OF ADVERSE DRUG REACTION (ADR) REPORTING

i. Suspected ADRs encountered should be reported for all products registered with DCA, i.e. pharmaceutical products, including biologics, Over–The-Counter (OTC) products, health supplements, and natural products. A separate guideline for healthcare providers entitled Garispanduan Farmakovigilans Vaksin untuk Anggota Kesihatan is available for further information. Any details pertaining Adverse Event Following Immunisation (AEFI), Garispanduan Farmakovigilans Vaksin untuk Anggota Kesihatan should be used as an ultimate reference.

ii. A reaction is suspected if the reporting healthcare professional, the PRH or any person who possess any registered product(s) believes that there is a possible causal relationship between the reaction and the product in question. If so, all available relevant clinical information must be provided.

iii. Adverse events, which are not suspected of being product-related by the healthcare professional attending to the patient, should not be reported unless the PRH feels that there is a possible causal relationship between the reaction and the product in question.

iv. All adverse reactions should be considered reportable according to the requirements outlined in this guidance document regardless of whether or not the product was used in accordance with the product information provided by the PRH.
P1.6 OBJECTIVES OF ADR MONITORING

The primary objectives of ADR monitoring are as follows:

i. To detect ADRs as early as possible especially serious, unknown and rare reactions;

ii. To establish the frequency and incidence of adverse reactions, both the well-recognised and newly discovered reactions;

iii. 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, and

iv. To maintain a database for sharing of information with regards to ADRs in this country.

P1.7 SPONTANEOUS ADR REPORTING

The WHO encourages reporting of ALL suspected ADRs. Health professionals are requested to report ADRs suspected to be related to all identifiable medicinal products including OTC products, health supplements, and natural products.

However, if healthcare professionals feel that it is cumbersome to report trivial, common and well-documented ADRs, they should particularly report reactions involving the following categories:

i. Serious ADRs

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

- Results in death;
- Life-threatening;
- 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.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Causes significant disability/incapacity;
- Causes congenital anomaly/birth defects.

ii. Suspected ADR(s) to medicinal products (including minor/common ADRs)

iii. Unexpected/unlabelled ADRs for all new and generic products.

iv. ADR(s) due to OTC product(s), health supplement(s) and natural product(s).

v. ADR(s) related to suspected drug-drug or drug-food interactions
vi. Change in frequency of a known ADR(s)

vii. ADR(s) involving special patient populations, e.g. pregnant, breastfeeding, elderly or paediatric patients

**P1.8 IMPACT OF ADR MONITORING**

**P1.8.1 Analysis and the Possible Outcomes of ADR Reports**

When an ADR report is analysed at the National ADR Monitoring Centre, NPRA and compared with other evidence, one of the following outcomes may be found:

i. 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.

ii. 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 thorough information to be given.

iii. No conclusion can be drawn and further data on other cases must be sought.

iv. The drug and the event were probably not associated.

**P1.8.2 Achievement of the primary objectives**

The primary objectives (See Section P1.6) will allow the following actions to be taken by:

i. The Authority

   a) Appropriate regulatory action in the interest of public health to minimise risk of ADRs for consumers;
   b) Make data available for drug analysis locally, to reduce the dependency on other countries;
   c) Promote rational drug usage;
   d) Promote the development of knowledge in this field, by sharing information with other countries via WHO.

ii. Product Registration Holders

   a) Initiate steps to make changes to the product dossier/information leaflets/labels;
   b) Make changes to product formulations or implement other product research and/or development strategies as necessary;
   c) Take measures to increase awareness of these findings.

The knowledge gained from ADR monitoring will also allow healthcare professionals to prescribe drugs rationally, while the public will be able to use medicinal products in an appropriate manner.
P1.9 GENERAL PRINCIPLES OF ADR REPORTING

P1.9.1 ADR Reporting Forms

The following are examples of ADR reporting forms available in Malaysia (Appendix 1):

i. Prepaid reporting blue form – for healthcare professionals
ii. Online reporting form – for healthcare professionals
iii. Consumer Side Effect Reporting Form (ConSERF) – for the general public
iv. Borang Pemantauan Kesan Sampingan Ringan Selepas Pelalian – specifically for parents/guardian or vaccinee for minor adverse event following immunisation
v. Suspect Adverse Reaction Report Form (CIOMS Form I) – for PRHs

P1.9.2 ADR Reporting Routes

ADR reports can be submitted to the Authority via the following routes:-

i. Post to:
The National Adverse Drug Reaction Monitoring Centre
National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia
Lot 36, Jalan Universiti
46200 Petaling Jaya
Selangor.

ii. Fax to: 03-79567151

iii. Email: fv@bpfk.gov.my


P1.9.3 Content of ADR Reports

i. The minimum information required for the submission of an ADR report:

   a) A named suspected drug
   b) A suspected reaction
   c) An identifiable patient
   d) An identifiable reporter

ii. If the data submitted in the report lacks any of the above essential information, the report cannot be assessed objectively and will not be entered into the Malaysian ADR database.

iii. Where possible, the specific brand name and the product registration number (MAL number) of the suspected product should be used. If it is not known, the generic name should be provided.
iv. Standard medical terminology should be used to describe the ADR. The use of vague terms should be avoided.

v. The PRH may comment on the consideration of causal association between the suspected product(s) and reactions(s) reported and should provide the criteria by which they have made the assessment before submission of the report(s).

P1.9.4 Follow-up Reports

i. Additional medically relevant information not available at the time of the initial report should be submitted in the form of follow-up reports (if necessary).

ii. 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 is the only reliable way to minimise the duplication of reports submitted to the Authority.

iii. The Authority may also request follow-up report(s) on a case-by-case basis, and reporters should provide the information whenever possible.

P1.10 ADR REPORTING TIMELINE

The timeline for ADR reporting differs by reporter category. Please refer to Appendix 2 for detailed information.
PART 2

GUIDELINE FOR HEALTHCARE PROFESSIONALS
PART 2: GUIDELINE FOR HEALTHCARE PROFESSIONALS

P2.1 BASIC PRINCIPLES OF ADR REPORTING

i. Report the event soon after it occurs (spontaneous reporting). A recent event is easier to report upon and the report is more likely to be accurate. Please refer to Appendix 2 for ADR reporting time frame and Garispanduan Farmakovigilans Vaksin untuk Anggota Kesihatan for AEFI.

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 have contributed towards the event, e.g. other concomitant drugs, herbal products, food supplements, chemicals, etc.

iv. A follow-up report should be submitted if any additional data becomes available later, e.g. if the same patient develops the effect again or if something happens which increases your suspicions or seems to exclude the effect.

v. In cases where a foetus or breastfed infant sustains an ADR, information on the mother and the child/foetus should be provided.

vi. Always write legibly.

vii. All reports must have the following four minimum data elements:

   a) A named suspected drug
   b) A suspected reaction
   c) An identifiable patient
   d) An identifiable reporter

viii. 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.

P2.2 CONFIDENTIALITY

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

P2.3 ADR REPORTING MECHANISM

i. Every healthcare facility may decide for itself how the ADR reporting systems should be operated and by whom. The arrangements will depend on the facilities’ own organisation and traditions. Ideally, the facilities’ Drugs and Therapeutics Committee should be informed of all ADRs, which occurred within their establishment.
ii. The healthcare professional who handled the medicinal product can act as a reporter, completing the reporting forms and sending them directly to the Authority.

iii. 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 otherwise.

iv. Healthcare professionals should report any ADRs encountered in patients where the products were used for off-label indications or in doses differing from the recommended doses, as this information will provide a better understanding of the product concern.

v. Reactions to unprocessed herbs should not be reported as these products are beyond the jurisdiction of the Authority.

vi. ADR reports may be submitted by using the pre-paid ADR forms which are supplied free of charge by the NPRA, or via online reporting (see Section P1.9.2 ADR Reporting Routes).

Figure 1 shows some suggestions of ADR reporting mechanism.
Figure 1: Suggestions of ADR Reporting Mechanism by Category of Reporters

ADR reporting

Reporting by Physician
- Ministry of Health Facility
- Private Health Facility

Reporting by Pharmacists
- Ministry of Health Facility
- Private Health Facility
- Retail Pharmacy

Reporting by Other Healthcare Professionals (e.g.: Medical Assistant, Nurse)
- Ministry of Health Facility
- Private Health Facility

Reporting by Product Registration Holder

Ministry of Health Hospital/Clinic Physician and Private Hospital Physician
The physicians act as reporters, completing the reporting forms themselves. Then the report should be submitted to a central point, preferably through the pharmacist. The central point should be in charge of collecting the forms, keeping a record, and sending them to the National ADR Monitoring Centre, NPRA.

Private Clinic Physician
The physicians act as reporters, completing the reporting forms themselves, keeping a record and sending them to the National ADR Monitoring Centre, NPRA.

Hospital/Clinic Pharmacist
The pharmacist acts as the reporter, completing the ADR forms in consultation with the physician. Since the source of ADR reporting may come from the physician, other healthcare professionals or direct from the patient, the pharmacist may play the role as a central point for National ADR Monitoring Centre, NPRA to contact whenever further information is required. In this situation, the pharmacist should:

i. retain all the tasks (collecting the forms, keeping a record, and sending the report);
ii. ensure the report is complete before sending to the NPRA;
iii. provide feedback received from NPRA back to the reporter.

Retail Pharmacist
Any adverse reactions encountered or reported by consumers must be reported and the pharmacist must ensure that all the necessary information must be available for the report submission.

The other healthcare professionals act as reporters, completing the reporting forms themselves. Then the report should be submitted to a central point, preferably the pharmacist. The central point should be in charge of collecting the forms, keeping a record, and sending them to the National ADR Monitoring Centre, NPRA.

The healthcare professionals may also provide the information on the ADR encountered to the product registration holder who will then report it to the National ADR Monitoring Centre NPRA.

However, the product registration holder must ensure that all the necessary information especially four data elements that are stated in P2.1 (vii) is available before submitting the report.
P2.4 REPORTING REQUIREMENTS IN SPECIAL SITUATIONS

P2.4.1 Reporting of Outcomes of Use during Pregnancy and Breastfeeding

i. Establish surveillance systems or follow up of pregnant or breastfeeding patient(s) for the purpose of collating experience on the usage and outcome of medicinal product used in these groups.

ii. Healthcare professional must report ALL ADR related to pregnancy and breastfeeding regardless of whether or not the drug is contraindicated in pregnancy.

iii. Reports on pregnancy should not be forwarded before the outcome is known unless unintended pregnancy is suspected as an adverse drug reaction.

iv. Healthcare 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. products taken before the gestational period need to be considered).

v. If, there is a signal of possible teratogenic effect (e.g. a cluster of similar abnormal outcomes) the National Adverse Drug Reaction Monitoring Centre, NPRA should be informed immediately.

P2.4.2 Director General of Health Approved Product

The prescriber of the product used as approved by the Director General of Health, must report all adverse drug reaction occurring with the use of the product, in the specified patients within the stipulated timeline as in Appendix 2.

P2.4.3 Compassionate Use/Named Patient Use

Where an organisation or a healthcare professional, supplying a medicinal product under compassionate use or named patient use, is notified or becomes aware of an ADR, it should be reported to the Authority the stipulated timeline as in Appendix 2.

P2.4.4 Lack of Efficacy

Reports of lack of efficacy should also be reported to the Authority. 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.
P2.4.5 Reporting of Overdoses

The healthcare professional should report cases of overdose (accidental or intentional) that lead to 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.
PART 3

ADR REPORTING GUIDELINE FOR
PRODUCT REGISTRATION
HOLDERS
PART 3: ADR REPORTING GUIDELINE FOR PRODUCT REGISTRATION HOLDERS

P3.1 REPORTING OBLIGATIONS

The legal provisions regarding the reporting of ADRs are set out in Regulation 28 of the Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment 2006), which state that:

The product registration holder or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction arising from the use of the registered product.

P3.2 SCOPE

i. This guidance document addresses the requirements for product registration holders (PRH) with regards to data collection and reporting of all suspected ADRs associated with medicinal products for human use registered in Malaysia.

ii. Recommendations regarding the reporting of emerging safety issues or of suspected ADRs occurring in special situations are also presented in this guidance document (see Section P3.7 and P3.9).

iii. Guidance provided includes the collection, management and reporting of events or patterns of use which do not result in suspected ADRs (e.g. asymptomatic overdose, abuse, off-label use, misuse or medication error) or which are not required to be reported as an individual case safety report (see Section P3.9.4). However, this information may need to be presented in Periodic Benefit-Risk Evaluation Reports (PBRER) for the benefit-risk evaluation of medicinal products. Please refer to Part 4 of this guidance document for further details.

P3.3 RESPONSIBILITIES OF THE PRODUCT REGISTRATION HOLDER

All PRHs must establish an appropriate system of pharmacovigilance (PV) in the company. This will ensure the company accepts responsibility and liability for its products on the market and appropriate action is taken, when necessary.

P3.3.1 The Basic PV System

PV system should consist at least of the following:-

i. Collection and management of data on product safety, including individual ADR reporting;

ii. An established system for signal detection of new or changing safety issues;

iii. Data evaluation and decision making with regards to safety issues;

iv. Pro-active risk management to minimise any potential risk associated with the use of a product;

v. Action to protect public health (including regulatory action);
vi. Communication with stakeholders and the public;

vii. Audit, both of the outcomes of action taken and the key processes involved.

**P3.3.2 Qualified Person Responsible for PV**

i. As part of the pharmacovigilance system, PRH shall have permanently and continuously at its disposal an appropriately qualified person responsible for PV activities. This person should have experience in all aspects of PV. If the identified person is not a healthcare professional, he/she should have access to a medically qualified person.

ii. The PRH must provide the Authority with the details of this qualified person (including full name, postal address, email address, telephone and fax numbers). Any changes of these details should be promptly informed.

iii. The qualified person shall act as the single PV contact point for the Authority, which is contactable whenever needed. The PRH should ensure there is a back-up personnel who is contactable whenever needed in the absence of the qualified person. The qualified person should ensure that the back-up person has all necessary information to fulfil the role.

iv. The roles of the qualified person responsible for PV are as follows:-

- To establish a system for monitoring ADRs associated with the use of products registered under the company.

- To ensure that information pertaining to ADRs which come to the knowledge of the company or organisation, including through medical representatives, is collected and collated so that it is accessible at a single point.

- To ensure that all local ADR reports are submitted to the Authority in a timely manner (see Appendix 2).

- To submit all relevant safety information such as Periodic Safety Update Reports (PSUR)/Periodic Benefit-Risk Evaluation Reports (PBRER), post-registration study reports and risk management plans (RMP).

- To ensure that any request for additional benefit-risk information by the Authority is answered fully and promptly, including sales data of the product(s) concerned.

- To alert the Authority of any emerging safety issue(s) involving products registered under the PRH (see Section P3.7).

**P3.3.3 Subcontracting of PV Activities**

i. There are situations where the PRH may subcontract certain activities of the PV system to third parties, such as to another organisation. The PRH shall nevertheless retain full responsibility in ensuring the quality, efficacy, and integrity of the PV system.
ii. This guidance document also applies to the other organisation to which the tasks have been subcontracted.

iii. When subcontracting tasks to another organisation, the PRH shall draw up detailed and up-to-date subcontracts. These should clearly document the contractual arrangements between the PRH and the other organisation, describing arrangements for delegation and the responsibilities of each party.

P3.4 ADR REPORTING SYSTEM

PRH should have in place written procedures describing the handling of all ADRs related to their products. The system and procedures in place must be adequate for receipt, handling, evaluation and reporting of ADRs to the Authority within the stipulated timelines (Appendix 2).

P3.4.1 Key Personnel In-Charge

The individual in-charge of the PV department should be qualified by pertinent training and experience relevant to their assigned responsibilities.

Requirements of the qualified person responsible for pharmacovigilance:

i. Knowledgeable on all applicable sections of this guidance document and the other related guideline(s).

ii. Responsible for establishing and managing a system which ensures information concerning all suspected ADRs that come to the knowledge of the company are collected and evaluated.

iii. Responsible for ensuring completeness of the reports (see Section P3.5.1).

iv. Readily available to evaluate information related to potential ADRs, to assess the seriousness, expectedness, and reportability of ADRs.

v. Responsible to determine if an ADR report qualifies for expedited reporting and if the report is to be included in the annual summary (see Section P3.10).

P3.5 ADR REPORTING

P3.5.1 Basic Principles of ADR Reporting

Only valid ADR reports qualify for reporting. All reports of suspected ADRs should therefore be validated before reporting them to the Authority, to ensure they contain the minimum criteria as below:
**P3.5.1.1 One or More Suspected Substance/Medicinal Product**

“Product” means:-

i. A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose;

or

ii. A drug to be used as an ingredient of a preparation for a medicinal purpose.

**P3.5.1.2 One or More Suspected Adverse Reaction**

A valid report should contain at least one specific ADR.

**P3.5.1.3 One Single Identifiable Patient**

Characterised by initials, patient identification number, date of birth, age, age group and/or gender. The information should be as complete as possible.

**P3.5.1.4 One or More Identifiable Reporter (Primary Source)**

i. Characterised by qualification (e.g. physician, pharmacist, other healthcare professional, consumer or other non-healthcare professional) name, initials or address. Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed.

ii. However, if the reporter does not wish to provide contact details, the ADR report(s) should still be considered as valid providing the organisation who was informed of the case is able to confirm it directly with the reporter.

iii. All parties providing case information or approached for case information should be identifiable, not only the initial reporter.

**P3.5.2 Others**

i. A report does not qualify as valid if only an outcome (e.g. death) or consequence (e.g. hospitalisation) is notified and no further information about the clinical circumstances is provided.

ii. If a PRH is made aware that a patient was hospitalised or died, without any further information, medical judgement should always be applied in deciding whether the notified information is an ADR or an event.

iii. The lack of any of the four elements mentioned in Section P3.5.1 means that the case is considered incomplete and does not qualify for reporting. PRHs are expected to exercise due diligence in following-up cases to collect the missing data elements (the same rule applies to the Authority if they received such incomplete cases directly from the reporter). Reports, for which the minimum information is incomplete, should nevertheless be recorded within the PV system for use in on-going safety evaluation activities.
P3.6 ADR REPORT BY SOURCE

P3.6.1 Unsolicited Reports

P3.6.1.1 Spontaneous Reporting

i. A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a PRH that describes one or more suspected ADRs in a patient who was given one or more medicinal products. This report should not be derived from a study or any organised data collection system where adverse event reporting is actively sought.

ii. Consumer ADR Reports

- Consumer ADR reports should be handled as spontaneous reports irrespective of any subsequent “medical confirmation” and PRH should attempt to obtain as much information as possible from the consumer.
- If the minimum reporting criteria are met and a qualified person from the PRH considers the report is relevant, the case is considered “reportable” and must be forwarded to the Authority. Reports that are not qualified for reporting must be documented and kept for future reference.

P3.6.1.2 Literature Reports

i. Scientific and medical literatures are a significant source of information for the monitoring of safety profile and benefit-risk balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues.

ii. PRHs should maintain awareness of related publications through a systematic literature review of widely used reference databases.

iii. PRHs should have procedures in place to monitor scientific and medical publications in journals, and to bring them to the attention of the PRH safety department as appropriate.

iv. A qualified healthcare professional from the PRH should use their clinical judgment to determine the appropriate frequency of literature searches based on the active ingredient(s) of products registered under the PRH.

v. Only ADRs which occurred in Malaysia, need to be reported to the Authority.

vi. If multiple products are mentioned in the publication, the PRH should consider only those, which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected ADR.

vii. One report should be created for each single patient identifiable based on characteristics provided in Section P3.5.1.3 Relevant medical information should be provided and the publication author(s) should be considered as the primary source(s).
viii. New and significant safety findings presented in these articles, for which reporting is not required, should however be discussed in the relevant sections of the concerned PBRER (see Part 4). Their overall impact on the product benefit-risk profile should be analysed. In addition, any new safety information which may affect the benefit-risk profile of a product should be notified immediately to the Authority.

**P3.6.1.3 Information on Suspected ADR from the Mass Media, Internet or Digital Media**

i. PRH should regularly screen mass media, internet or digital media for potential reports of suspected ADR. The frequency of the screening should allow potential valid ADR to be reported to the Authority within the stipulated timelines (Appendix 2).

ii. Although not exhaustive, the following list should be considered as digital media: website, web page, blog, vlog, social network, internet forum, chat room, health portal.

iii. PRH may also consider utilising their websites to facilitate the collection of suspected ADR reports.

iv. Unsolicited cases of suspected ADR from the mass media, internet or digital media should be handled as spontaneous reports. The same reporting periods as for spontaneous reports should be applied.

v. When collecting reports of suspected ADRs via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient (see Section P3.5.1.3).

vi. When one party (the Authority or PRH) is made aware that the primary source may also have reported the suspected ADR to another concerned party, the report should still be considered valid. All the relevant information necessary for the detection of the duplicate case should be included in the ADR report(s).

**P3.6.2 Solicited Reports**

Solicited reports are defined by the ICH as those derived from organised data collection systems, which include clinical trials, registries, post-approval named-patient-use programs, other patient support and disease management programs, surveys of patients or healthcare professionals, or information gathering on efficacy or patient compliance.

Solicited reports do not originate with any safety issue or safety study, but invariably arise in the course of interaction with patients for unrelated purposes. ADR reports obtained from any of these sources should not be considered unsolicited. Such reports are regarded as solicited in nature and one cannot infer implied causality, the convention for spontaneous reports.
P3.6.2.1 Compassionate Use/Named Patient Use

i. Where an organisation (e.g. sponsor, applicant, PRH, hospital or wholesaler) or a healthcare professional is supplying a medicinal product under ‘compassionate use’ or ‘named patient use’, it should be strictly controlled and be subject to protocol.

ii. The protocol should encourage the prescriber to report any adverse reactions suspected of being related to use of the medicinal product to the Authority. The organisation supplying the medicinal product should continuously monitor the balance of benefit and risk of drugs used under such conditions.

P3.6.2.2 PRH Sponsored Studies

i. Studies subject to post-market ADR reporting requirements (e.g. phase IV studies) should be monitored in a way that ensures that all serious expected and unexpected ADRs, including unusual failure in efficacy for new drugs, are reported to the PRH by the investigator(s) so that the PRH can provide such reports to the Authority.

ii. Investigators should be provided with the definition of what constitutes an ADR for reporting purposes. In such cases, it is important to try to distinguish between “reactions” and “events”, not only for administrative purposes but also to minimise the instances of reporting adverse events that are clearly unrelated to therapy.

iii. PRH should help investigators understand their role in assessing the possible relationship between an adverse event and the administration of a product during post-marketing studies.

iv. Comparator and concomitant products used in these studies are within the scope of this guidance document. It is the sponsor’s responsibility to decide whether active comparator and concomitant product cause the ADRs should be reported to the other PRH and/or directly to the Authority.

P3.6.2.3 Non-PRH Sponsored Studies

i. PRH may receive ADR reports from studies where its product was a comparator treatment (and therefore used in accordance with approved labelling) or was a product the patient was taking concomitant to the study medication but was suspected of causing an ADR.

ii. The source of these reports may be another PRH who is sponsoring the study, a private investigator or an academic centre. The PRH must apply all principles outlined in this guidance document pertaining to reporting requirements, including determination of seriousness, causality, and minimal criteria for submitting an ADR report. The PRH should not alter the causality assessment of the trial product(s) provided by the trial sponsor and should include any narrative of the trial sponsor regarding causality, if available. The PRH should assess causality on its own marketed health product(s).
P3.6.2.4 Post-Study Adverse Reactions

Although such information is not routinely sought or collected by the sponsor, serious adverse reactions that occurred after the patient had completed a clinical study may possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment is needed to decide whether expedited reporting is required.

P3.7 EMERGING SAFETY ISSUES

Events may occur, which do not fall within the definition of reportable valid individual case reports, and thus are not subject to the reporting requirements, even though they may lead to changes in the known benefit-risk balance of a medicinal product and/or impact on public health. Examples include:

i. Major safety findings from a newly completed non-clinical study.
ii. Major safety concerns identified in the course of a non-interventional post-authorisation study or of a clinical trial.
iii. Signal of a possible teratogenic effect or significant hazard to public health.
iv. Safety issues published in the scientific and medical literature.
v. Safety issues arising from the signal detection activity or emerging from a new individual case safety report (ICSR) and which impact on the benefit-risk balance of the medicinal product and/or have implications for public health.
vi. Safety issues related to the use outside the terms of the product registration.
vii. Safety issues due to misinformation in the product information.
viii. Product registration withdrawal, non-renewal, revocation or suspension outside the country concerned for safety-related reasons.
ix. Urgent safety restrictions outside the country concerned.
ox. Safety issues in relation to the supply of raw material.

These events/observations, which may affect the benefit-risk balance of a medicinal product, are not to be submitted as individual case reports. They should be notified in writing to the Authority as Emerging Safety Issues and this should be done immediately when the PRH is made aware of them.

This written notice should indicate the points of concern and the actions proposed in relation to authorisation for the concerned product. Those safety issues should also be analysed in the relevant sections of the PBRER of the authorised product.

P3.8 MANAGEMENT OF ADR REPORTS

P3.8.1 Evaluation of ADR Reports

i. Unique identifier should be assigned to each suspected ADR case for traceability.
ii. For ADR reports to qualify for expedited reporting, the four (4) minimum criteria for submitting a case, as listed in P3.5.1 must be met.

iii. The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting. Competent PRH are expected to exercise due diligence in following-up the cases to collect the missing data elements.

iv. A mechanism of ADR evaluation should be in place, including but not limited to seriousness and expectedness assessment, which would ensure expedited reporting timelines are met.

v. Reports, for which the minimum information is incomplete or when a case is not reportable, justification should be provided and the case documented within the PV system for use in on-going safety evaluation activities.

vi. ADR reports should be appropriately coded. Standard international terminology such as The Medical Dictionary for Regulatory Activities (MedDRA) is recommended to code ADR reports.

P3.8.2 Reports of ADR Cases from Two or More Sources

i. A mechanism should be in place to identify ADR data that were reported to the PRH more than once.

ii. When similar reports are found, verifications should take place to determine if they are duplicate reports.

iii. Multiple copies of the same ADR reports should be nullified within the PV system and the record of nullification should be maintained, allowing for auditing of the nullified record in the future.

iv. Documented procedures and processes should be in place describing when ADR reports may be nullified.

v. Documentation related to nullified cases should be retained.

P3.8.3 ADR Description

i. The objective of the narrative is to summarise all relevant clinical and related information, including patient characteristics, therapy dates, medical history, clinical course of the event(s), diagnosis, and ADR(s) including the outcome, laboratory evidence (including normal ranges), and any other information that supports or refutes an ADR (e.g. rechallenge information). The narrative should serve as a comprehensive, stand-alone "medical story".

ii. Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records including summarised relevant autopsy or post-mortem findings should be included in the report, and their availability should be mentioned in the narrative and supplied on request. A qualified healthcare professional from the PRH should exercise clinical judgment to determine what information should be submitted.
P3.8.4 Follow-up Information

i. Follow-up information should be actively sought and submitted as it becomes available for appropriate amendments to the database in the Authority. Follow-up ADR reports should be clearly labelled as such.

ii. Specific reference should be made to the initial report by including the PRH number specific to the initial report in the follow-up report. Follow-up information should be clearly identified, and should be updated in the narrative sequentially by the date it was received by the PRH.

iii. In any scheme to optimise the value of follow-up, the first consideration should be prioritisation of case reports by importance. The priority for follow-up of ADR cases should be as follows:
- Serious and unexpected;
- Serious and expected;
- Non-serious and unexpected.

iv. Although non-serious and unexpected cases are not expedited, PRHs are encouraged to pursue follow-up information on these reports. In addition, cases of "special interest" also deserve extra attention as high priority (e.g. ADRs under enhanced or active surveillance at the request of the Authority) as well as any cases that might lead to a labelling change.

P3.9 REPORTING REQUIREMENTS IN SPECIAL SITUATIONS

P3.9.1 Use of a Medicinal Product during Pregnancy or Breastfeeding

PRHs must establish surveillance systems of pregnant or breastfeeding patients for the purpose of collating experience on the usage and outcome of products used in these groups.

PRHs must report ADRs related to pregnancy and breastfeeding regardless of whether or not the product is contraindicated in this situation. Reports on pregnancy should not be forwarded unless the outcome is known or unintended pregnancy is suspected as an ADR.

P3.9.1.1 Pregnancy

i. Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context, the use of standard structured questionnaires is recommended.

ii. Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported. This especially refers to:
- Reports of congenital anomalies or developmental delay in the foetus or the child;
- Reports of foetal death and spontaneous abortion;
• Reports of suspected ADRs involving neonates.

iii. Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports, which have a normal outcome, should not be reported since there is no suspected ADR. These reports should however be collected and discussed in the PSUR/PBRER (see Part 4).

iv. PRHs are expected to follow-up all reports of pregnancies where the foetus could have been exposed to 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. products taken before the gestational period may need to be considered).

v. If a PRH becomes aware of a signal of possible teratogenic effect (e.g. a cluster of similar abnormal outcomes) the Authority should be informed in writing immediately.

**P3.9.1.2 Breastfeeding**

Suspected ADR(s), which occur in infants following exposure to a medicinal product from breast milk, should be reported in accordance with the criteria outlined in this guidance.

**P3.9.2 Use of a Medicinal Product in Paediatric or Elderly Population**

The collection of safety information in the paediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a healthcare professional or consumer reports a case. This will enable the identification of potential safety signals specific to a particular population.

**P3.9.3 Lack of Efficacy**

i. Reports of lack of efficacy should also be submitted to the Authority. Judgment should be used in reporting.

ii. In certain circumstances, such as medicinal products used in critical conditions or for the treatment of life-threatening illnesses, vaccines and contraceptives, reports of lack of therapeutic efficacy may require to be reported within the stipulated timeline (Refer Appendix 2).

iii. This applies unless the reporter has specifically stated that the outcome was due to disease progression and not related to the medicinal product.

iv. Clinical judgment should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting. For example, an antibiotic used in a life-threatening situation where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a life-threatening infection, where the lack of therapeutic efficacy appears to be due to the development of a newly-resistant strain of a bacterium previously regarded as susceptible, should be reported within the stipulated timeline (Refer Appendix 2).
v. For vaccines, cases of lack of therapeutic efficacy should be reported, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccines, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of therapeutic efficacy by a healthcare professional might constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorisation safety studies as appropriate.

P3.9.4 Reports of Overdose, Abuse, Off-Label Use, Misuse, Medication Error or Occupational Exposure

i. For the purpose of this guidance, medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

ii. Reports of overdose (accidental or intentional), abuse, off-label use, misuse, medication error or occupational exposure, which lead to an ADR, should be reported to the Authority.

iii. Reports with no associated ADR should not be reported as individual case reports. They should be considered in PBRER as applicable (see Part 4). When those reports constitute safety issues affecting the benefit-risk balance of the medicinal product, they should be notified to the Authority (see Section P3.7 Emerging Safety Issue).

iv. They should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, and context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

P3.10 SUMMARY REPORTS

i. The PRH must, whenever requested by the Authority, conduct a concise, critical analysis of the ADRs and serious ADRs to a product and prepare a summary report of all the ADR reports received during the previous twelve months.

ii. The selected 12-month period for the summary report is specified by the PRH. The summary report is to be maintained by the PRH on-site, should be easily accessible and, when requested, it is to be submitted to the Authority.

iii. When the Authority requests the annual summary report, it is preferred that it be submitted in the format in accordance with the standards defined in Appendix 3.

iv. The PRH must determine whether there has been a significant change in what is known about the risks and benefits of the product. If the PRH concludes from the annual summary report that there has been a significant change, the PRH must inform the Authority in writing, immediately. Examples may include a significant change in the frequency or severity of a known risk or the identification of a previously unknown risk.
P3.11 ADVERSE DRUG REACTIONS OCCURRING OUTSIDE MALAYSIA

i. Foreign individual case reports should not be forwarded to the Authority on a routine basis, but should be reported in the context of a specific safety issue or on specific request by the Authority.

ii. The Authority 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 CALENDAR DAYS of first knowledge by the PRH.

iii. Information on withdrawal/suspension of the registration status in any country should be notified to the Authority within 24 HOURS of first knowledge by the PRH.
PART 4

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)
PART 4: PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

P4.1 INTRODUCTION

i. The Periodic Benefit-Risk Evaluation Report (PBRER) described in this guidance document is intended to be a common standard for periodic benefit-risk evaluation on marketed products. The required format and content of PBRER are based on ICH Guideline E2C (R2). The PBRER replaces the Periodic Safety Update Report (PSUR) format previously described in the Malaysian Guidelines for Reporting and Monitoring (Edition 2002) and ICH Guideline E2C (R1). In this document, the report shall be described and named as PBRER. In the event where only PSUR or PSUR addendum report is prepared for submission, PRHs will have to incorporate a critical evaluation of the benefit-risk balance either in the PSUR and PSUR addendum reports or in an attachment to the cover letter.

ii. When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials.

iii. Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

iv. In clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events which are too rare to occur in clinical trials may be observed (e.g. severe liver injury). These factors underline the need for continuing analysis of relevant safety, efficacy and effectiveness information throughout the lifecycle of a medicinal product promptly, as important findings occur and periodically to allow an overall assessment of the accumulating data.

v. Although the majority of new information will be safety related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the medicinal product place in therapy may be pertinent to its benefit-risk assessment.

P4.2 OBJECTIVES

P4.2.1 Main Objective

The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the product, and on its benefit in approved indications, to enable an appraisal of the product’s overall benefit-risk profile.

P4.2.2 General Information of PBRER

The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the PRH during the reporting interval, in the context of cumulative information by summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product:
i. Summarising any important new efficacy/effectiveness information that has become available during the reporting interval;

ii. Examining whether the information obtained by the PRH during the reporting interval is in accord with previous knowledge of the medicinal product’s benefit and risk profile;

iii. Where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications;

iv. When appropriate, the PBRER should include proposed action(s) to optimise the benefit-risk profile. Urgent safety information should be reported through the appropriate mechanism; the PBRER is not intended to be used to provide initial notification of significant new safety information or to provide the means by which new safety concerns are detected.

P4.3 GENERAL PRINCIPLES

P4.3.1 Submission of PBRER for New Drug Products/Biologics: Post Registration

The PBRER should provide information on all approved indications, dosage forms, and regimens for the product, with a single Data Lock Point (DLP). In some circumstances, it will be appropriate to present data by indication, dosage form, dosing regimen, or population (e.g. children vs. adults) within the relevant section(s) of the PBRER.

In exceptional cases, submission of separate PBRERs might be appropriate. For example, a product used in two formulations for systemic and topical administration in entirely different indications. In these cases, the Authority should be notified and their agreement obtained, preferably at the time of approval.

P4.3.2 Submission of PBRER for Generic Scheduled Poison, Generic Non-Scheduled Poison, Health Supplement and Natural Products

As a general rule, PBRERs for these medicinal products are not required to be submitted. But, it is expected that PRH will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts the benefit-risk balance or the product information.

P4.3.3 Reference Information

An objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product’s benefit and risk profile, and to indicate whether changes should be made to the reference product information.

The reference product information for the PBRER would include “core safety” and “approved indications” components. In order to facilitate the assessment of benefit and benefit-risk by indication in the evaluation sections of the PBRER, the reference product information document should list all approved indications in other countries.
The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarised in Section 17.1 (“Important Baseline Efficacy/Effectiveness Information”) of the PBRER.

The following possible options can be considered by PRHs in selecting the most appropriate reference product information for a PBRER:

**P4.3.3.1 Company Core Data Sheet (CCDS)**

It is a common practice for PRHs to prepare their own CCDS, which includes sections relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option is for PRHs to use the latest CCDS in effect at the end of the reporting interval as the reference product information for both the risk sections of the PBRER as well as the main approved indications for which benefit is evaluated.

When the CCDS for a medicinal product does not contain information on approved indications, the PRH should clearly specify which document is used as the reference information for the approved indications in the PBRER.

**P4.3.3.2 Other Options for the Reference Product Information**

When there is no CCDS or CCSI for a product, e.g. where the product is approved in only one country or region or for established/generic products on the market for many years, the PRH should clearly specify the reference information being used. This may comprise product information from reference country.

Where the reference information for approved indications is a separate document to the Reference of Safety Information (RSI), the version in effect at the DLP of the PBRER should be included as an appendix to the PBRER (see Section P4.5.20).

The PRH should continuously evaluate whether any revision of the reference product information/RSI is needed whenever new safety information is obtained throughout the reporting interval. Significant changes to the reference product information/RSI made during the interval should be described in Section 4 (“Changes to Reference Safety Information”) of the PBRER and include:

i. Changes to contraindications, warnings/precautions sections of the RSI;

ii. Addition of ADR(s) and interactions;

iii. Addition of important new information on use in overdose;

iv. Removal of an indication or other restrictions for safety or lack of efficacy reasons.

Significant changes to the RSI made after the DLP but before submission of the PBRER should be included in Section 14 (“Late-Breaking Information”) of the report, if feasible.
P4.3.4 Level of Detail within PBRER

The level of detail provided in certain sections of the PBRER should depend on the medicinal product’s known or emerging important benefits and risks. This approach is applicable to those sections of the PBRER in which there is an evaluation of safety data, efficacy/effectiveness data, safety signals, and benefit-risk. Therefore, the extent of information provided in such PBRER sections will vary among individual PBRERs.

For example, when there is important new safety information, a detailed presentation of that information should be included, plus the relevant benefit information, in order to facilitate a robust benefit-risk analysis. Conversely, when little new important safety information has become available during the reporting interval, a concise summary of baseline benefit information should be sufficient, and the benefit-risk evaluation would consist primarily of an evaluation of updated interval safety data.

P4.3.4.1 Efficacy/Effectiveness

For the purpose of this guidance document, evidence on benefits in clinical trials and in everyday medical practice should be reported. Because the terms are not harmonised across countries, the terms ‘efficacy/effectiveness’ are used in this guidance document to clarify that information from both clinical trials and everyday medical practice are within the scope of the information on benefit to be included within the PBRER. In some regions, efficacy refers to evidence of benefit from controlled clinical trials while effectiveness implies use in everyday medical practice.

P4.3.4.2 Benefit-Risk Evaluation

When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks. As new information about the drug emerges during marketing experience, benefit-risk evaluation should be carried out to determine whether benefits continue to outweigh risks, and to consider whether steps need to be taken to improve the benefit-risk balance through risk minimisation activities, e.g. labelling changes, communications with prescribers, or other steps.

P4.3.5 Periodicity and PBRER Data Lock Point

P4.3.5.1 International Birth Date (IBD) and Data Lock Point (DLP)

Each medicinal product should have an IBD: IBD is the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world. When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), the date of the first marketing approval for any of the various approvals should be regarded as the IBD and, therefore, determine the DLP for purposes of the PBRER.

The DLP is the date designated as the cut-off for data to be included in a PBRER. Through PBRERs prepared with harmonised DLPs based on a
common IBD, the same updated safety and benefit-risk information can be reviewed globally by different regulatory authorities. When a separate PBRER is prepared for a fixed combination product, the DLP for that PBRER can be based on either the earliest IBD of one of the component active substances, or the IBD of the first marketing approval anywhere in the world for the fixed combination.

**P4.3.5.2 Managing Different Frequencies of PBRER Submission**

The need for the submission of a PBRER usually depends on factors such as approval dates, the length of time the product has been on the market, and the extent of knowledge of the benefit-risk profile of the product.

The PBRER’s format and content are intended to apply to periodic reports that cover reporting periods of 6 months or longer.

PRH in addition may be requested to submit PBRER in the following circumstances – new indication, new combination of drugs, new dosage form, new routes of administration or use in populations beyond the registration for the active ingredient.

An ad hoc PBRER may be requested by the Authority (see Section P4.3.5.3 of this guidance document).

Independent of the length of the interval covered by the report, each PBRER should be stand-alone and reflect new and cumulative information currently available to the PRHs.

Use of a single harmonised IBD and DLP for each product is important in order to reduce the burden of work involved in preparing PBRERs, and respects the original purpose of the PBRER – to prepare a single worldwide summary on a product that can be submitted to different regulatory authorities.

As part of post-registration requirement for newly approved products in Malaysia, PRH is required to routinely submit PBRERs, 6 monthly for the first 2 years after approval and annually for the subsequent 3 years. The first PBRER submitted should have DLP no later than 6 months after approval in Malaysia.

Sections that provide interval information are likely needed to be updated for each PBRER, and the content used in the previous PBRER can be reviewed and reused for sections where no new information has arisen since preparation of the last PBRER, if appropriate. Following review, it may be determined that sections providing evaluation of cumulative data may not need to be updated if the content remains up to date with current information.

**P4.3.5.3 Ad hoc PBRERs**

Ad hoc PBRERs are reports outside the routine reporting requirements. Whenever ad hoc report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the PRH.
P4.3.5.4 Time Interval between Data Lock Point and the Submission

As a result of the expanded scope of the PBRER, the time interval between the DLP and submission of PBRERs should be as follows:

i. PBRERs covering intervals of 6 or 12 months: within 70 calendar days;

ii. ad hoc PBRERs: 90 calendar days, unless otherwise specified in the ad hoc request.

The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission.

P4.4 FORMAT AND PRESENTATION OF PBRER

P4.4.1 Format

The recommended format and content of the PBRER, including table of contents, section numbering, and content of each section, are outlined below.

P4.4.2 Presentation

The recommended table of contents, including section numbering, for the PBRER is provided below:

i. Title Page

ii. Executive Summary

iii. Table of Contents

1. Introduction

2. Worldwide Marketing Approval Status

3. Actions Taken in the Reporting Interval for Safety Reasons

4. Changes to Reference Safety Information

5. Estimated Exposure and Use Patterns

   5.1 Cumulative Subject Exposure in Clinical Trials

   5.2 Cumulative and Interval Patient Exposure from Marketing Experience

6. Data in Summary Tabulations

   6.1 Reference Information

   6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

   6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

7. Summaries of Significant Findings from Clinical Trials during the Reporting Period

   7.1 Completed Clinical Trials

   7.2 Ongoing Clinical Trials
7.3 Long-Term Follow-up
7.4 Other Therapeutic Use of Medicinal Product
7.5 New Safety Data Related to Fixed Combination Therapies
8. Findings from Non-Interventional Studies
9. Information from Other Clinical Trials and Sources
10. Non-Clinical Data
11. Literature
12. Other Periodic Reports
13. Lack of Efficacy in Controlled Clinical Trials
14. Late-Breaking Information
15. Overview of Signals: New, Ongoing, or Closed
16. Signal and Risk Evaluation
   16.1 Summary of Safety Concerns
   16.2 Signal Evaluation
   16.3 Evaluation of Risks and New Information
   16.4 Characterisation of Risks
   16.5 Effectiveness of Risk Minimisation (if applicable)
17. Benefit Evaluation
   17.1 Important Baseline Efficacy/Effectiveness Information
   17.2 Newly Identified information on Efficacy/Effectiveness
   17.3 Characterisation of Benefits
18. Integrated Benefit-Risk Analysis for Approved Indications
   18.1 Benefit-Risk Context — Medical Need and Important Alternatives
   18.2 Benefit-Risk Analysis Evaluation
19. Conclusions and Actions
20. Appendices
P4.5 GUIDANCE ON CONTENTS OF THE PBRER

All sections should be completed, and when no information is available, it should be stated.

Title Page

The title page of the PBRER should include the following information:
- Date of the report;
- Medicinal product(s);
- IBD;
- Reporting interval;
- PRH(s) name(s) and address(es);
- Any statement on the confidentiality of the information included in the PBRER.

Executive summary

This section should provide a concise summary of the most important information contained in the report.

The following information should be included in the Executive Summary:
- Introduction;
- Reporting interval;
- Medicinal product(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration and formulation(s);
- Estimated cumulative exposure of clinical trial subjects; interval and cumulative post-approval exposure;
- Number of countries in which the medicinal product is approved;
- Summary of overall benefit-risk evaluation [based on Section 18.2 (“Benefit-Risk Analysis Evaluation”) of the PBRER];
- Actions taken or proposed for safety reasons, e.g. significant changes to the reference product information, other risk minimisation activities;
- Conclusions.

Table of Contents

P4.5.1 Section 1: Introduction

Section 1 of the PBRER should include:
- IBD;
- reporting interval;
• medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration and formulation(s);
• a brief description of the approved indication(s) and population(s);
• a brief description and explanation of any information that has not been included in the PBRER;
• the rationale for submission of multiple PBRERs for the medicinal product, if applicable.

P4.5.2 Section 2: Worldwide Marketing Approval Status

Section 2 of the PBRER should provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved, if applicable.

P4.5.3 Section 3: Actions Taken in the Reporting Interval for Safety Reasons

Section 3 of the PBRER should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the PRH, sponsor of a clinical trial(s), regulatory authorities, data monitoring committees, or ethics committees that had a significant influence on the benefit-risk profile of the approved medicinal product.

P4.5.4 Section 4: Changes to Reference Safety Information

Section 4 of the PBRER should list any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, adverse drug reactions (ADRs), overdose, and interactions; important findings from ongoing and completed clinical trials;* and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PBRER.

A clean version of the reference document that is current at the DLP of the PBRER should be included. A track change version of the reference information is not required.

P4.5.5 Section 5: Estimated Exposure and Use Patterns

This section of the PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. Section 5.1 of the PBRER should provide information on cumulative exposure in clinical trials.

Section 5.2 should provide cumulative and interval exposure in the marketed setting. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used across PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PBRER introducing the change.
P4.5.5.1 Section 5.1: Cumulative Subject Exposure in Clinical Trials

Section 5.1 of the PBRER should include the following information, if applicable, presented in tabular format (see Appendix 4, Tables 1-3 for examples):

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the development international birth date (DIBD), the date of first approval for the conduct of an interventional clinical trial in any country. It is recognised that for older products, precise data might not be available.

- More detailed cumulative subject exposure in clinical trials should be presented if available, e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development programme.

- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.

- If clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate.

- When there are substantial differences in duration of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in duration of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years).

- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.

- If the serious adverse events (SAEs) from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.

- For individual trials of particular importance, demographic characteristics should be provided separately.

P4.5.5.2 Section 5.2: Cumulative and Interval Patient Exposure from Marketing Experience

Separate estimations should be provided for interval exposure (since the DLP of the previous PBRER) and, when possible, cumulative exposure (since the IBD). See Appendix 4 (Table 4 and 5) for examples. The estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive
them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to estimate patient exposure.

The data should be presented according to the following categories:

i. Post-approval (non-clinical trial) exposure:
   - An overall estimation of patient exposure should be provided.
   - In addition, the data should be routinely presented by indication, sex, age, dose, formulation, and region, where applicable.
   - Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.
   - When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

ii. Post-approval use in special populations:

   Where post-approval use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:
   - Paediatric population;
   - Elderly population;
   - Pregnant or lactating women;
   - Patients with hepatic and/or renal impairment;
   - Patients with other relevant co-morbidity;
   - Patients with disease severity different from that studied in clinical trials;
   - Subpopulations carrying relevant genetic polymorphism(s);
   - Patients of different racial and/or ethnic origins.

iii. Other post-approval use:

   If the PRH becomes aware of patterns of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, drug abuse, misuse, and use beyond that recommended in the reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Such patterns may be regional.
If known, the PRH may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available.

For purposes of identifying patterns of use outside the terms of the reference product information, the PRH should use the appropriate sections of the reference product information that was in effect at the DLP of the PBRER (e.g. approved indication, contraindications).

P4.5.6 Section 6: Data in Summary Tabulations

PBRER Sections 6.1 to 6.3 should present cumulative summary tabulations of serious adverse events (SAEs) from clinical trials and post-marketing sources that have been reported to the PRH since the DIBD. At the discretion of the PRH, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

P4.5.6.1 Section 6.1: Reference Information

Section 6.1 of the PBRER should specify the version(s) of the coding dictionary used for analyses of adverse reactions.

P4.5.6.2 Section 6.2: Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

In this section of the PBRER, should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events (SAEs) reported in the PRH’s clinical trials, from the DIBD to the DLP of the current PBRER. The PRH should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by system organ class (SOC), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

Appendix 4 (Table 6) of this guidance document provides an example of summary tabulations of SAEs from clinical trials. The following points should be considered:

- In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious; they should not include non-serious events.

- When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level and SOC should be presented in the summary tabulations.

- The tabulations should include blinded and unblinded clinical trial data. Unblinded SAEs might originate from completed trials and
individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors/PRHs should not unblind data for the specific purpose of preparing the PBRER.

- Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

- Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all SAEs for the investigational drug, active controls, and placebo. It may be useful to give rates by dose.

**P4.5.6.3 Section 6.3: Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources**

Section 6.3 of the PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the DLP of the current PBRER. The tabulations should include:

- Serious and non-serious adverse drug reactions from spontaneous ADR reports, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities;
- Serious adverse reactions from non-interventional studies;
- Solicited reports of serious adverse reactions.

The tabulations should include interval and cumulative data presented side-by-side (see Appendix 4, Table 7) and should be organised by SOC.

For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. This section should not serve to provide analysis or conclusions based on the data presented.

**P4.5.7 Section 7: Summaries of Significant Safety Findings from Clinical Trials during the Reporting Interval**

This section of the PBRER should provide a brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the PRH’s sponsored clinical trials that became available during the reporting interval of the report.
The safety signals arising from clinical trial sources should be tabulated in Section 15 (“Overview of Signals: New, Ongoing, or Closed”) of the PBRER. Evaluation of the signals (whether or not categorised as refuted signals or either potential* or identified risks”) that were closed during the reporting interval should be presented in Section 16.2 (“Signal Evaluation”) of the PBRER.

New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in Section 16.3 (“Evaluation of Risks and New Information”) and Section 16.4 (“Characterisation of Risks”), respectively. Findings from clinical trials not sponsored by the PRH should be described in the relevant sections of the PBRER.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in approved indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illnesses should be summarised in Section 13 (“Lack of Efficacy in Controlled Clinical Trials”) of the PBRER.

When possible and relevant, data categorised by sex and age (particularly children versus adult), indication, dose, and region should be presented.

A listing of any PRH-sponsored post-marketing interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval should be included in an appendix. The listing should include the following information for each trial:

- Study ID (e.g. protocol number or other identifier);
- Study title (abbreviated study title, if applicable);
- Study type (e.g. randomised clinical trial, cohort study, case-control study);
- Population studied (including country and other relevant population descriptors, e.g. paediatric population or trial subjects with impaired renal function);
- Study start (as defined by the PRH) and projected completion dates;
- Status:
  - Ongoing (clinical trial has begun);
  - Completed (clinical study report is finalised).

**P4.5.7.1 Section 7.1: Completed Clinical Trials**

Section 7.1 should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.
**P4.5.7.2 Section 7.2: Ongoing Clinical Trials**

If the PRH is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

**P4.5.7.3 Section 7.3: Long-Term Follow-Up**

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products.

**P4.5.7.4 Section 7.4: Other Therapeutic Use of Medicinal Product**

This section of the PBRER should include clinically important safety information from other programmes conducted by the PRH that follow a specific protocol, with solicited reporting (e.g. expanded access programmes, compassionate use programmes, particular patient use, single-patient investigational new products, treatment investigational new products, and other organised data collection).

**P4.5.7.5 Section 7.5: New Safety Data Related to Fixed Combination Therapies**

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the product that is the subject of a PBRER is also approved or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from use of the combination therapy.

- If this PBRER is for a fixed combination product, this section should summarise important safety information arising from the individual components.

The information specific to the combination can be incorporated into a separate section(s) of the PBRER for one or all of the individual components of the combination.

**P4.5.8 Section 8: Findings from Non-Interventional Studies**

This section should summarise relevant safety information or information with potential impact on the benefit or risk evaluations, from PRH-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when applicable to multiple regions.
A listing of any PRH-sponsored post-marketing non-interventional study(ies) with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures that were completed or ongoing during the reporting interval should be included in an appendix (see Section P4.5.7 of this guidance document for the information that should be included in the listing).

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the report where stipulated by regional requirements.

P4.5.9 Section 9: Information from Other Clinical Trials and Sources

P4.5.9.1 Section 9.1: Other Clinical Trials
This subsection should summarise information accessible to the PRH with reasonable and appropriate effort from any other clinical trial/study sources, including results from pooled analyses or meta-analyses of randomised clinical trials, and safety information provided by co-development partners or from investigator-initiated trials.

P4.5.9.1 Section 9.2: Medication Errors
This subsection should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient.

Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process, and may involve patients, consumers, or healthcare professionals.

This information may be received by the PRH via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

Signals or risks identified from any information source and/or category of reports should be presented and evaluated in the relevant section of the PBRER.

P4.5.10 Section 10: Non-Clinical Data
This section should summarise major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g. carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designed to address specific safety concerns should be included in the PBRER, regardless of the outcome. Implications of the findings presented in PBRER Section 10 should be discussed in the relevant evaluation sections of the report.
P4.5.11 Section 11: Literature

This section should summarise new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved medicinal product that the PRH became aware of during the reporting interval. Literature searches for PBRERs should be wider than those for individual adverse reaction cases, and include studies reporting safety outcomes in groups of subjects. If relevant, information on active substances of the same class should be considered.

P4.5.12 Section 12: Other Periodic Reports

Unless otherwise specified by national or regional regulatory requirements, the PRH should prepare a single PBRER for a single active substance. However, if a PRH prepares multiple PBRERs for a single active substance (e.g. covering different indications, or formulations), this section should summarise significant findings from the other periodic reports if they are not presented elsewhere within this report.

When available, based on contractual agreements, the PRH should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors, PRHs, other contractual partners).

P4.5.13 Section 13: Lack of Efficacy in Controlled Clinical Trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to the treated population and should be summarised in this section.

P4.5.14 Section 14: Late-Breaking Information

This section should summarise information on potentially important safety and efficacy/effectiveness findings that arise after the DLP but while the PBRER is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the PRH, a data monitoring committee, or a regulatory authority has taken for safety reasons. New individual case reports should not be included unless they are considered to constitute an important index case (i.e. the first instance of an important event), an important safety signal, or where they may add information to the evaluation of safety concerns already presented in the PBRER (e.g. a well-documented and unconfounded case report of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow).

Any significant change proposed to the reference product information which has occurred after the DLP of the report but before submission should also be included in this section, where feasible. Such changes could include a new contraindication, warning/precaution, or new adverse drug reaction.
The data presented in this section should also be taken into account in the evaluation of risks and new information (see Section P4.5.16.3 of this guidance document).

P4.5.15 Section 15: Overview of Signals: New, Ongoing, or Closed

The general location for presentation of information on signals and risks within the PBRER is shown in Appendix 6 of this guidance document. The purpose of Section 15 of the PBRER is to provide a high level overview of safety signals that were closed (i.e. the evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation, at the end of reporting interval.

For the purposes of the PBRER, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the PRH. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific drug/event combination as a validation step is required. Signals may be qualitative (e.g. a pivotal individual safety case report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a regulatory authority.

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation involve medical judgement and scientific interpretation of available data, which is presented in Section 16 (“Signal and Risk Evaluation”) of the PBRER.

A new signal is a signal that the PRH became aware of during the reporting interval. New clinically important information on a previously closed signal that became available during the reporting period of the PBRER (i.e. a new aspect of a previously refuted signal or recognised risk likely to warrant further action to verify) would also constitute a new signal. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the DLP of the PBRER. Examples would include new information on a previously:

- Closed and refuted signal, which would result in the signal being re-opened;
- Identified risk which is indicative of a clinically significant difference in the severity of the risk, e.g. transient liver enzyme increases are identified risks and new information is received indicative of a more severe outcome such as hepatic failure; neutropenia is an identified risk and a well-documented and unconfounded case report of agranulocytosis is received;
- Identified risk for which a higher frequency of the risk is newly found, e.g. in a subpopulation;
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

Within this section, or as an appendix, include a tabular listing of all signals ongoing or closed at the DLP of the PBRER. This table should include the following information. See Appendix 5 for an example.
P4.5.16 Section 16: Signal and Risk Evaluation

The purpose of Section 16 of the PBRER is to provide:

- A succinct summary of what is known about important identified and potential risks and important missing information at the beginning of the reporting interval covered by the PBRER;
- An evaluation of all signals closed during the reporting interval;
- An evaluation of new information with respect to previously recognised identified and potential risks;
- An updated characterisation of important potential and identified risks, where applicable;
- A summary of the effectiveness of risk minimisation activities in any country or region.

Appendix 6 of this guidance document provides a flowchart to illustrate the mapping of signals and risks to specific sections of the PBRER.

The evaluation subsections should not summarise or repeat information presented in previous sections of the PBRER, but should instead provide an interpretation of the information, with a view towards characterising the profile of those risks assessed as important.

As a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PBRER; however, when integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance
belonging to a class known to be associated with this adverse reaction) should be provided.

**P4.5.16.1 Section 16.1: Summary of Safety Concerns**

The purpose of this section is to provide a summary of safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. These comprise:

- Important identified risks;
- Important potential risks;
- Important missing information.

The following factors should be considered when determining whether or not a risk is important:

- Medical seriousness of the risk, including the impact on individual patients;
- Its frequency, predictability, preventability, and reversibility;
- Potential impact on public health (frequency and size of treated population);
- Potential for avoidance of a medical product with a preventive benefit as a result of public perception of risk.

For products with an existing safety specification, this section can be either the same as, or be derived from, the safety specification summary at the start of the reporting interval of the current PBRER. For products without an existing safety specification, this section should provide information on the important identified and potential risks and important missing information associated with use of the product, based on pre- and post-approval experience. Important identified and potential risks may include, for example:

- Important adverse reactions;
- Interactions with other medicinal products;
- Interactions with foods and other substances;
- Medication errors;
- Effects of occupational exposure;
- Pharmacological class effects.

The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

**P4.5.16.2 Section 16.2: Signal Evaluation**

This section of the PBRER should summarise the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either
because it is refuted or because it is determined to be a potential or identified risk, following evaluation.

The two main categories to be included in this sub-section are:

i. Those signals that, following evaluation, have been refuted as “false” signals based on medical judgement and scientific evaluation of the currently available information.

ii. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the PRH.

It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

- Closed and refuted signals;
- Closed signals that are categorised as important potential risks;
- Closed signals that are categorised as important identified risks;
- Closed signals that are potential risks not categorised as important;
- Closed signals that are identified risks not categorised as important.

Where applicable the closed signal evaluations can be presented by indication or population.

The description(s) of the signal evaluations can be included in this section of the PBRER, or in an appendix. Each signal evaluation should include the following information as appropriate:

- Source of the signal;
- Background relevant to the evaluation;
- Method of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms [e.g. PTs, HLTs, SOCs, etc.] or Standardised MedDRA Queries [SMQs] that were reviewed), and analytical approaches;
- Results – a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an ICSR, e.g. an index case of well documented agranulocytosis or Stevens-Johnson syndrome;
- Discussion;


- **Conclusion.**

PRH's evaluations and conclusions for refuted signals should be supported by data and clearly presented.

**P4.5.16.3 Section 16.3: Evaluation of Risks and New Information**

This section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in Section 16.2 ("Signal Evaluation") of the PBRER.

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the tabular summary in Appendix 5 and evaluated in Section 16.2 of the PBRER, if the signal is also closed during the interval of the PBRER.

Updated information on a previously recognised risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information that allows further characterisation of a previously recognised risk.

New information can be organised as follows:

- New information on important potential risks;
- New information on important identified risks;
- New information on other potential risks not categorised as important;
- New information on other identified risks not categorised as important;
- Update on important missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PBRER. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in Section 16.4 of the report. It is recommended that the level of detail of the evaluation included in this section should be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of new information and missing information update(s) can be included in this section of the PBRER, or in an appendix. Each evaluation should include the following information as appropriate:

- Source of the new information;
- Background relevant to the evaluation;
- Method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- Results – a summary and critical analysis of the data considered in the risk evaluation;
- Discussion;
• Conclusion including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in Section 16.4 ("Characterisation of Risks") of the PBRER.

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.

**P4.5.16.4 Section 16.4: Characterisation of Risks**

This section will characterise important identified and important potential risks based on cumulative data (i.e. not restricted to the reporting interval), and describe important missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

• Frequency;
• Numbers of cases (numerator); precision of estimate, taking into account the source of the data;
• Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
• Estimate of relative risk; precision of estimate;
• Estimate of absolute risk; precision of estimate;
• Impact on the individual patient (effects on symptoms, quality or quantity of life);
• Public health impact;
• Patient characteristics relevant to risk (e.g. age, pregnancy/lactation, disease severity, hepatic/renal impairment, relevant co-morbidity, genetic polymorphism);
• Dose, route of administration;
• Duration of treatment, risk period;
• Preventability (i.e. predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
• Reversibility;
• Potential mechanism;
• Strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.

For PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by
indication, formulation, or route of administration. Headings that could be considered include:

- Risks relating to the active substance;
- Risks related to a specific formulation or route of administration (including occupational exposure);
- Risks relating to a specific population;
- Risks associated with non-prescription use (for substances that are available as both prescription and non-prescription products).

**P4.5.16.5 Section 16.5: Effectiveness of Risk Minimisation (If Applicable)**

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section.

Insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarised by region, if applicable and relevant.

When required for reporting in a PBRER, results of evaluations that are relevant to only one region and that became available during the reporting interval should be provided in regional appendices.

**P4.5.17 Section 17: Benefit Evaluation**

PBRER Sections 17.1 and 17.2 provide the baseline and newly identified benefit information that support the characterisation of benefit described in Section 17.3 that in turn supports the benefit-risk evaluation in Section 18 ("Integrated Benefit-Risk Analysis for Authorised Indications").

**P4.5.17.1 Section 17.1: Important Baseline Efficacy/Effectiveness Information**

This section summarises information on the efficacy/effectiveness of the medicinal product as of the beginning of the reporting interval, and provides the basis for the benefit evaluation. This information should relate to the approved indication(s) of the medicinal product listed in the reference product information (see Section P4.3.3).

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors, where relevant.

The level of detail provided in this section should be sufficient to support the characterisation of benefit in PBRER Section 17.3 and the benefit-risk assessment in Section 18.
P4.5.17.2 Section 17.2: Newly Identified Information on Efficacy/Effectiveness

New information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section. For approved indications, new information on efficacy/effectiveness under conditions of actual use should also be described in this section, if available. New information about efficacy/effectiveness in uses other than the approved indication(s) should not be included, unless relevant for the benefit-risk evaluation in the approved indication. Information on indications approved during the reporting interval should also be included in this section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in Section 17.3 and the benefit-risk assessment in Section 18.

New information on efficacy/effectiveness might also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g. vaccines, emergence of resistance to anti-infective agents.

P4.5.17.3 Section 17.3: Characterisation of Benefits

Section 17.3 of the PBRER provides an integration of the baseline benefit information and any relevant new benefit information that became available during the reporting interval for approved indications.

This section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy/effectiveness, considering the following, when available:

- A brief description of the strength or evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
- New information that challenges the validity of a surrogate endpoint, if used;
- Clinical relevance of the effect size;
- Generalisability of treatment response across the indicated patient population, e.g. information that demonstrates lack of treatment effect in a sub-population;
- Adequacy of characterisation of dose-response;
- Duration of effect;
- Comparative efficacy;
- A determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medical practice.

The level of detail provided in PBRER Section 17.3 should be sufficient to support the analysis of benefit-risk in Section 18.

When there are no new relevant benefit data, this section should provide a characterisation of the information in Section 17.1 of the PBRER.
When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.

P4.5.18 Section 18: Integrated Benefit-Risk Analysis for Approved Indications

Whereas PBRER Sections 16.4 ("Characterisation of Risks") and 17.3 ("Characterisation of Benefits") present the risks and benefits, respectively, Section 18 should provide an integration and critical analysis of the key information in these sections as described below. Section 18 provides the benefit-risk analysis, and should not simply duplicate the benefit and risk characterisation presented in Sections 16.4 and 17.3.

P4.5.18.1 Section 18.1: Benefit-Risk Context – Medical Need and Important Alternatives

This section should provide a brief description of the medical need for the medicinal product in the approved indications, and summarise alternatives (medical, surgical, or other; including no treatment).

P4.5.18.2 Section 18.2: Benefit-Risk Analysis Evaluation

A benefit-risk profile is specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible. The evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should take into account the following points:

- Whereas previous sections will include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.

- Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated.

- With respect to key benefit(s), consider its nature, clinical importance, duration, and generalisability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).

- With respect to risk, consider its clinical importance, e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.

- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe
how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

- The assumptions, considerations, and judgment or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.

Economic considerations (e.g. cost-effectiveness) should not be included in the benefit-risk evaluation. When there is important new information or an ad hoc PBRER has been requested, a detailed benefit-risk analysis is warranted.

Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

P4.5.19 Section 19: Conclusions and Actions

This section should provide a conclusion about the implications of any new information that arose during the reporting interval, in terms of the overall benefit-risk evaluation, for each approved indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the PRH should assess the need for further changes to the reference product information and propose changes as appropriate.

In addition and as applicable, the conclusion should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance, for further discussion with the relevant regulatory authorities. This may include proposals for additional risk minimisation activities.

These proposals should also be considered for incorporation into the risk management plan.

P4.5.20 Section 20: Appendices to the PBRER

The PBRER should be accompanied by the following appendices, as appropriate, numbered as follows:

- Reference Information;
- Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials and Interval/Cumulative Summary Tabulations from Marketed Experience;
- Tabular Summary of Safety Signals (if not included in the body of the report);
- Listing of interventional and non-interventional studies with a primary objective of post-authorisation safety monitoring;
• List of the Sources of Information Used to Prepare the PBRER (when desired by the PRH).

The PBRER may also be accompanied by regional appendices, as needed, to fulfil national and regional requirements.
PART 5

RISK MANAGEMENT PLAN (RMP)
PART 5: RISK MANAGEMENT PLAN (RMP)

P5.1 INTRODUCTION

i. A medicinal product is registered on the basis that in the specified indication(s), at the time of registration, the benefit-risk balance is judged to be positive for the target population. A typical medicinal product will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact.

ii. However, not all actual or potential risks will have been identified at the time when an initial registration is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post-registration. Planning of the necessary pharmacovigilance activities to characterise the safety profile of the medicinal product will be improved if it is more closely based on specific issues identified from pre- or post-registration data and from pharmacological principles.

iii. Risk management is a global activity. However, because of differences in indication and healthcare systems, target populations may be different across the world and risk minimisation activities will need to be tailored to the system in place in a particular country or global region.

iv. In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a medicinal product may also vary between regions. Therefore a product may have different versions of a Risk Management Plan (RMP) for each region although there will be core elements which are common to all.

v. The purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible. Therefore, risk management has three stages, which are inter-related and re-iterative:

a) Characterisation of the safety profile of the medicinal product including what is known and not known.

b) Planning of pharmacovigilance activities to characterise risks, identify new risks, and increase the knowledge in general about the safety profile of the medicinal product.

c) Planning and implementation of risk minimisation and mitigation and assessment of the effectiveness of these activities.

vi. The risk management, is applicable to medicinal products at any point in their life cycle. However, this guidance is applicable to post-authorisation risk management. The risks addressed in this guidance are those related to non-clinical and clinical safety. In addition, quality issues may be relevant if they affect the safety and/or efficacy of the product.
P5.2 STRUCTURES AND PROCESS

P5.2.1 Terminology

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include:

i. An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;

ii. An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;

iii. An adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be placebo, active substance or non-exposure.

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.

Examples include:

i. Toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;

ii. Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of, but is not large enough to suggest a causal relationship;

iii. A signal arising from a spontaneous adverse reaction reporting system;

iv. An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

Missing information

Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.
Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

**Important identified risk and important potential risk**

An identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health.

What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the Contraindications or Warnings and Precautions section of the product information should be considered important.

**Risk management system**

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions.

**Risk management plan**

A detailed description of the risk management system.

**Risk minimisation activity (used synonymously with risk minimisation measure)**

A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur.

**Safety concern**

An important identified risk, important potential risk or important missing information.

**P5.2.2 Principles of Risk Management**

The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks.
P5.3 RESPONSIBILITIES OF PRODUCT REGISTRATION HOLDER (PRH) FOR RISK MANAGEMENT

In relation to risk management of its medicinal products, PRH is responsible for:

i. Ensuring that it constantly monitors the risks of its medicinal products and reports the results of this, as required, to the Authority;

ii. Taking all appropriate actions to minimise the risks of the medicinal products and maximise the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available.

iii. Producing a RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts.

iv. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals.

v. Since a risk management plan is primarily a pharmacovigilance document, ideally the production of it should be managed by personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure.
vi. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the applicant/product registration holder who should ensure oversight by someone with the appropriate scientific background within the company.

P5.4 OBJECTIVES OF A RISK MANAGEMENT PLAN

i. The main objectives of RMP are to:-

a) Identify or characterise the safety profile of the medicinal product(s) concerned;

b) Indicate how to characterise further the safety profile of the medicinal product(s) concerned;

c) Document measures to prevent or minimise the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;

d) Document post-authorisation obligations that have been imposed as a condition for registration.

ii. There is a requirement to fulfil these obligations, a RMP should also:

a) Describe what is known and not known about the safety profile of the concerned medicinal product(s)

b) Indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies);

c) Include a description of how the effectiveness of risk minimisation measures will be assessed.

iii. The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products. For products requiring Periodic Benefit-Risk Evaluation Report (PBRER), certain (parts of) modules may be used for both purposes.

P5.5 SITUATIONS WHEN A RISK MANAGEMENT PLAN SHOULD BE SUBMITTED

P5.5.1 RMP for New Drug Products/Biologics

i. An RMP or an update, as applicable, may need to be submitted at any time during a product’s life-cycle.

ii. RMP or an update will normally be expected, with an application involving a significant change to an existing registered product:

- New dosage form;
- New route of administration;
- New manufacturing process of a biotechnologically-derived product;
• Paediatric indication;
• Other significant change in indication.

iii. A significant change in indication is a change of approved indication(s) of a product where the new treatment target population differs materially from the one for which the product was previously approved. This includes (but is not limited to):

• A new disease area, a new age group (e.g. paediatric indication),
• A move from severe disease to a less severely affected population,
• 2nd line or other therapy,
• At the request of the Authority when there is a concern about a risk affecting the benefit-risk balance,
• At the time of the renewal of the product registration if the product has an existing risk management plan.

An updated RMP should always be submitted if there is a significant change to the benefit-risk balance of one or more medicinal products included in the RMP.

P5.5.2 Submission of RMP for Generic Scheduled Poison, Generic Non-Scheduled Poison, Health Supplement and Natural Products

As a general rule, RMPs for these medicinal products are not required to be submitted. But, it is expected that PRH will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts the benefit-risk balance or the product information. However, a RMP may be requested when there are safety concerns affecting the benefit-risk assessment that require specific risk minimisation activities.

P5.6 STRUCTURE OF THE RISK MANAGEMENT PLAN

The RMP consists of seven parts. Certain parts of the RMP, in particular the safety specification, are subdivided into modules, so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PBRERs).

The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the important risks and important uncertainties of the product.
Figure 3: Overview of the parts and modules of the RMP

Part I Product(s) overview

Part II Safety specification

  Module SI Epidemiology of the indication(s) and target population(s)
  Module SII Non-clinical part of the safety specification
  Module SIII Clinical trial exposure
  Module SIV Populations not studied in clinical trials
  Module SV Post-authorisation experience
  Module SVI Identified and potential risks
  Module SVII Summary of the safety concerns

Part III Pharmacovigilance plan

Part IV Plans for post-authorisation efficacy studies

Part V Risk minimisation measures (including evaluation of the effectiveness on risk minimisation measures)

Part VI Summary of the risk management plan

Part VII Annexes

P5.6.1 RMP Part I: Product Overview

This should provide the administrative information on the RMP and an overview of the product(s) covered within it.

The information should include:

Active substance information:

  • Active substance(s);
  • Pharmacotherapeutic group(s) (ATC code);
  • Name of PRH or applicant;
  • Date and country of first authorisation worldwide (if applicable);
  • Date and country of first launch worldwide (if applicable);
  • Number of medicinal product(s) to which this RMP refers.

Administrative information on the RMP:

  • Data Lock Point of the current RMP;
  • Date submitted and the version number;
  • List of all parts and modules of the RMP with date and version of the RMP when the part/module was last (updated and) submitted.

and
For each medicinal product included in the RMP:

- Invented name(s);
- Brief description of the product including:
  - Chemical class;
  - Summary of mode of action;
  - Important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- Indications;
- Dosage;
- Pharmaceutical forms and strengths.

**P5.6.2 RMP Part II: Safety Specification**

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include what is known and not known about the medicinal product(s).

It should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. It should also address the populations potentially at risk (where the product is likely to be used i.e. both labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-authorisation period.

In the RMP, the safety specification will form the basis of the pharmacovigilance plan, and the risk minimisation plan.

**P5.6.2.1 Module SI: Epidemiology of the Indication(s) and Target Population(s)**

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, but the emphasis should be on the epidemiology in the country of the proposed indication.

**P5.6.2.2 Module SII: Non-Clinical Part of the Safety Specification**

This RMP module should present a summary of the important non-clinical safety findings, for example:

- Toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- General pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system);
- Drug interactions;
- Other toxicity-related information or data.

**P5.6.2.3 Module SIII: Clinical Trial Exposure**

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables/graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient-years, patient-months) exposed to the medicinal product. This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations). Stratifications would normally include:

- Age and gender;
- Indication;
- Dose;
- Racial origin.

Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format.

The exposure of special populations (pregnant women, breastfeeding women, renal impairment, hepatic impairment, cardiac impairment, subpopulations with relevant genetic polymorphisms, immunocompromised) should be provided as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the genetic polymorphism.

The categories above are only suggestions and tables/graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicinal product where only one indication has been studied, and route of administration, number of courses/immunisations or repeat administrations may be important categories to be added.

**P5.6.2.4 Module SIV: Populations Not Studied in Clinical Trials**

RMP module SIV should discuss which subpopulations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population.

Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. This is particularly important when exclusion criteria are not proposed as contraindications for the drug.

Lists of inclusion/exclusion criteria should not be provided by trial, but a summary of the effect of these in the overall development programme in relation to the target population should be provided. In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences may arise through trial setting.
(e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria.

The implications, with respect to predicting the safety of the product in the marketplace, of any of these populations with limited or no research should be explicitly discussed. In addition, the limitations of the database with regard to the detection of adverse reactions due to:

- Number of patients studied;
- Cumulative exposure (e.g. specific organ toxicity);
- Long term use (e.g. malignancy);

should be discussed. Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.

Populations to be considered for discussion should include (but might not be limited to):

- **Paediatric population**
  
  Children (from birth to 12 years old) and adolescent (13 -18 years old) or, if justified, to other developmentally meaningful groups i.e. taking into account specific organ maturation). If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.

- **Elderly population**
  
  Implications for use in patients over the age of 65 should be discussed – with appropriate consideration given to use in the older end of the age spectrum.

  The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist.

  The cumulative effect of multiple impairments and multiple medications should be discussed. Consideration of whether particular laboratory screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. In particular any adverse reactions which might be of special concern in the elderly e.g. dizziness or central nervous system effects should be explored.

- **Pregnant or breastfeeding women**
  
  If the target population includes women of child-bearing age, the implications for pregnancy and/or breastfeeding should be discussed. If the medicinal product is not specifically for use during pregnancy, any pregnancies which have occurred during the developmental programme and their outcomes should be discussed.
For products where pregnancy should be avoided for safety reasons, the discussion on pregnancy should also include an analysis of the reasons why the contraceptive measures in place during the clinical trials failed and the implications for use in the less controlled conditions of everyday medical practice.

- **Patients with hepatic impairment**
- **Patients with renal impairment**
- **Patients with other relevant co-morbidity (e.g. cardiovascular or immunocompromised including organ transplant patients)**
- **Patients with disease severity different from that studied in clinical trials**

Any experience of use in patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity.

- **Subpopulations carrying known and relevant genetic polymorphism**

The extent of pharmacogenetic effects and the implications on genetic biomarker use in the target population should be discussed. Where a proposed drug indication constitutes patients with or without specific genetic markers, or the clinical development programme has been in patients with a specific mutation, the PRH should discuss the implications of this for the target population and explore whether use in patients with an unknown or different genotype could constitute a safety concern.

If a potentially clinically important genetic polymorphism has been identified but not fully studied in the clinical development programme, this should be considered as missing information and/or a potential risk. This should be reflected in the safety specification and pharmacovigilance plan. Whether it is included as a safety concern for the purposes of risk minimisation will depend upon the importance of the possible clinical implications.

- **Patients of different racial and/or ethnic origins**

Genetic variants can influence pharmacodynamics and pharmacokinetics, and subsequently affect the efficacy and/or safety of the administered drug. Inter-ethnic differences in drug efficacy and safety have been observed in different ethnic groups due to e.g. genetic polymorphisms.

Major inter-ethnic differences in pharmacokinetics of drugs may also occur due to types and/or frequencies of gene variants coding for drug metabolising enzymes. The consequences of these inter-ethnic differences could be that the proportion of subjects with particular beneficial effects or adverse reactions varies, leading to different benefit-risk profiles and specific recommendations in these ethnic populations.
The experience of drug use in patients with different racial and/or ethnic origins should be discussed including the implications on efficacy and safety, based on pharmacokinetics and pharmacodynamics, in the target population.

If it is likely that efficacy or safety may be affected by race or ethnicity, consideration should be given to including this either as a safety concern or as a topic for inclusion in RMP P5.6.4. Consideration should also be given as to whether post-authorisation efficacy and/or safety studies are necessary.

**P5.6.2.5 Module SV: Post-Authorisation Experience**

**SV.1  Action taken by regulatory authorities and/or product registration holders for safety reasons**

List any significant regulatory action (including those initiated by the product registration holder), in any market, taken in relation to a safety concern.

Significant regulatory action would include: a restriction to the approved indication, a new contraindication, a new or strengthened warning or any action to suspend or revoke a product registration.

This list should be cumulative, and specify the country, action taken and the date as appropriate. Roll-out in multiple countries of a new safety statement initiated by the PRH can be presented as one action.

When the RMP is updated, a brief description of the reasons leading to any significant actions since the last submission of the RMP should be provided. It may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations as authorised in the country.

**SV.2  Non-study post-authorisation exposure**

Where marketing of the medicinal product has occurred, the PRH should provide cumulative data on patients exposed post-marketing. Where possible, the information should be stratified by relevant variables.

These may include age, sex, indication, dose and region/country. Depending upon the medicinal product, other variables may be relevant such as number of vaccination courses, route of administration or duration of treatment.

When deciding which measure to use for exposure data, it is important to consider the way a medicinal product is used. Exposure data based on the number of kilogrammes of medicinal product sold divided by the average dose is only valid if the medicinal product is always used at one dose level for a fixed length of time, which is not the situation with most medicinal products.

In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other
measures should be used. For example, for medicinal products used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate.

If the drug has different routes of administration, e.g. subcutaneous or oral, exposure data should be presented separately, where possible. Competent authorities may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, product registration holders should consider routinely providing such data where possible.

A more accurate breakdown of drug exposure based on market research should be provided where possible.

If a drug utilisation study has been performed, for reimbursement or other reasons, the results, as they reflect use in the real world setting, should be provided.

**SV.3 Post-authorisation off-label use**

Post-marketing updates to the safety specification should include information on country off-label use; i.e. the intentional use, for a medical purpose, which is not in accordance with the approved product information for a medicinal product.

Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. This includes drug utilisation studies which were requested by national competent authorities for purposes other than risk management. When off-label use is a safety concern or a concern has been raised by the competent authorities regarding off-label use, product registration holders should attempt to quantify such use along with a description of the methods used to arrive at these figures.

**SV.4 Epidemiological study exposure**

Product registration holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures.

This listing should include studies undertaken by the product registration holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the PRH has been sent the results by a third party, should also be included.

Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if
appropriate) and study status (completed or on-going) should be provided.

If a study has been published, a reference should be included in this RMP section, a synopsis should be included in RMP Annex 5 and the publication provided in RMP Annex 12.

**P5.6.2.6 Module SVI: Identified and Potential Risks**

This RMP module provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

**SVI.1 Newly identified safety concerns**

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below.

The source of the safety concern should be stated, whether it is an important identified or important potential risk and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

**SVI.2 Recent study reports with implications for safety concerns**

Study reports (either interim or final, from whichever type of study), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate.

**SVI.3 Details of important identified and potential risks from clinical development and post-authorisation experience**

This RMP section should provide more information on the important identified and potential risks. This RMP section should be concise and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents in package insert or CDS.

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and which is/is likely to be included in the Contraindications or Warnings and Precautions section of the package insert/CDS should be included here.

In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person’s life, and which could lead to serious consequences if untreated
should also be considered for inclusion, e.g. severe nausea and vomiting with chemotherapy.

For some products, disposal of the used product may constitute a safety concern, e.g. transdermal patches where there may be significant amounts of active substance remaining in the patch when it is discarded. There may also be occasions where there is an environmental concern over product disposal because of known harmful effects on the environment, e.g. substances which are particularly hazardous to aquatic life which should not be disposed of in landfill sites.

Presentation of risk data:

When the information is available, detailed risk data should include the following:

- Frequency;
- Public health impact (severity and seriousness/reversibility/outcomes);
- Impact on the individual patient (effect on quality of life);
- Risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- Preventability (i.e. predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- Potential mechanism;
- Evidence source(s) and strength of the evidence.

The frequency of important identified risks should be expressed taking into account the source of the data. For a product already on the market, the reporting rate based on the number of spontaneously reported adverse events/adverse reactions (in the numerator) and the sales data (in the denominator) is very likely to underestimate the rate of occurrence of an adverse reaction in an exposed population and should be avoided.

When an accurate frequency is needed for an important identified risk, this should always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number of patients exposed to the medicinal product and the number of patients who experienced the respective identified risk are known.

Where appropriate, the period of major risk should be identified. Identified risk incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess (relative incidence compared to a specified comparator group) should be given. Time to event data should be summarised using survival techniques. Cumulative hazard functions may also be used to represent the cumulative probability of occurrence of an adverse reaction in the presence of competing events.
For potential risks, the background incidence/prevalence in the target population(s) should be provided.

For most RMPs involving single products, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns, e.g. accidental intravenous administration could be a safety concern in a single product with both oral and subcutaneous forms.

For RMPs covering multiple products where there may be significant differences in the identified and potential risks for different products, it may be appropriate to categorise the risks to make it clearer which risks relate to which product. Headings, which could be considered, include:

- Risks relating to the active substance
  
  This would include important identified or potential risks which are common to all formulations, routes of administration and target populations. It is likely that most risks will fall into this category for the majority of products.

- Risks related to a specific formulation or route of administration
  
  Examples might include an RMP with two products: one a depot intramuscular formulation and the other an oral formulation. Additional concerns relating to accidental intravenous administration clearly would not be applicable to the oral product.

- Risks relating to a specific target population
  
  The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a product intended solely for adult patients.

- Risks associated with switch to non-preservation status.
  
  Division of identified and potential risks using headings should only be considered when the risks clearly do not apply to some products and lack of separation could cause confusion.

**P5.6.2.7 Module SVI: Identified and Potential Interactions Including Food-Drug and Drug-Drug Interactions**

**SVI.1 Identified and potential interactions including food-drug and drug-drug interactions**

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, and also in relation to commonly used medications in the target population.

For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed
for the different indications and in the different populations should be discussed. Interactions which are important clinically should be included as a safety concern in RMP module SVIII "Summary of the safety concerns."

SVI.2 Pharmacological class effects

Important risks which have not been included in RMP module SVII "Details of important identified and potential risks from clinical development and post-authorisation experience" (above) but which are believed to be common to the pharmacological class should be discussed here. The discussion should include the mechanism, the impact (severity and duration), frequency seen with other members of the same or similar pharmacological class.

If there is evidence that a risk, which is common to other members of the pharmacological class, is not thought to be a safety concern with the concerned medicinal product, details, and the evidence supporting this, should be provided and discussed.

P5.6.2.7 Module SVII: Summary of the Safety Concerns

At the end of the safety specification a summary should be provided of the safety concerns. A safety concern may be an:

- Important identified risk;
- Important potential risk; or
- Important missing information.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, similar to the presentation of risks in RMP module SVI, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- Safety concerns relating to the active substance;
- Safety concerns related to a specific formulation or route of administration;
- Safety concerns relating to the target population;
- Risks associated with switch to non-prescription status.

Division of safety concerns by headings should only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

It is recommended that applicants/product registration holders follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development programme.
Elements which might need to be incorporated include:

- Quality aspects if relevant in relation to the safety and efficacy of the product;
- The disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches);
- Innovative pharmaceutical forms or;
- Use with a medical device.

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible.

P5.6.3 RMP Part III: Pharmacovigilance plan

P5.6.3.1 Objective of Pharmacovigilance Plan

The purpose of the pharmacovigilance plan is to discuss how the PRH plans to identify and/or characterise the risks identified in the safety specification. It provides a structured plan for:

- The identification of new safety concerns;
- Further characterisation of known safety concerns including elucidation of risk factors;
- The investigation of whether a potential safety concern is real or not;
- How important missing information will be sought.

The pharmacovigilance plan should be based on the safety concerns summarised in RMP module SVIII of the safety specification. It is important to note that only a proportion of risks are likely to be foreseeable and therefore signal detection, which is part of routine pharmacovigilance, will be an important element in identifying new risks for all products.

Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the PRH should list their planned pharmacovigilance activities for that concern.

Pharmacovigilance plans should be proportionate to the risks of the product. If routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies) “routine pharmacovigilance” should be entered against the safety concern.
**P5.6.3.2 Post-Authorisation Safety Studies**

- Studies to measure the effectiveness of risk minimisation measures

Post-authorisation safety studies (PASS), which measure the effectiveness of risk management measures and should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan.

- Drug utilisation studies

- Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry).

**P5.6.4 RMP Part IV: Plans for Post-Authorisation Efficacy Studies**

Efficacy, as assessed at the time of authorisation, is based on data from clinical trials which, by their nature, are of relatively limited duration (e.g. usually between 6 months-3 years). The benefit (efficacy of the medicine) risk balance must be positive for a medicine to be authorised. Whereas it is recognised that many risks will be identified post authorisation, there is an implicit assumption that efficacy remains relatively constant over time. This may not always be valid.

For many medicines there will not be a need for post-authorisation efficacy studies. However, there may be circumstances where efficacy may vary over time and also patients in whom this assumption of constant efficacy may not be true and where longer term efficacy data post authorisation is necessary.

**P5.6.4.1 Summary of Existing Efficacy Data**

As background to any proposed post-authorisation efficacy studies, and to provide context for the summary of the RMP, there should be a summary of the efficacy of the product and the studies and endpoints on which it was based. Where the RMP covers more than one medicinal product, the information should be provided by medicinal product to permit easy extraction for the summary of the RMP module.

Similarly medicinal products with more than one indication should have a separate summary of efficacy for each one.

The summary of efficacy (one page maximum per indication/population) should be in lay language and the following should be considered for inclusion:

- Current (gold) standards of treatment;
- Where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse etc.);
- A brief statement of the standard against which the medicine was judged;
- Number of patients in pivotal studies and treatment regimens;
- Results in lay language.

The following areas should be discussed briefly and the need for further studies post authorisation evaluated:

- The robustness of the endpoints on which the efficacy evaluation is based;
- Applicability of the efficacy data to all patients in the target population;
- Factors which might affect the efficacy of the product in everyday medical practice;
- Variability in benefits of treatment for sub populations.

For updates to the RMP, any subsequent data which impacts on efficacy should be mentioned and its impact on the benefits of the medicinal product discussed.

**P5.6.5 RMP Part V: Risk Minimisation Measures**

On the basis of the safety specification, applicants/product registration holders should assess what risk minimisation activities are needed for each safety concern. The risk minimisation plan should provide details of the risk minimisation measures which will be taken to reduce the risks associated with individual safety concerns.

It is not possible to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population. A safety concern may be addressed using more than one risk minimisation measure.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product. Examples when multiple risk minimisation plans could be considered include:

- An active substance where there are products with both prescription only and non-prescription legal status;
- Medicinal products where there are major risks, and the indications cross areas of medical expertise. In the latter case, there could be diverse educational needs for different specialists since the areas of specialised knowledge will be distinct. For example an active substance which causes important QT prolongation would most likely not need educational material explaining the implications of this and the interactions with other products if the product were intended solely for use by cardiologists in a hospital setting but might need educational material if intended for use in general practice or orthopaedic surgery where it is unlikely that prescribers will have this specialist knowledge;
• Active substances where there are major risks which differ according to the target population.

Risk minimisation activities may consist of routine risk minimisation (e.g. measures associated with locally approved package insert) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective.

P5.6.5.1 Routine Risk Minimisation

Routine risk minimisation activities are those which apply to every medicinal product. These relate to:

• Package insert;
• Product label(s);
• Consumer Medication Information Leaflet (RiMUP)
• Pack size(s);
• Legal status of the product.

P5.6.5.2 Additional Risk Minimisation Activities

Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.

P5.6.5.3 Summary of Risk Minimisation Measures

A table summarising the routine and additional risk minimisation activities by safety concern should be provided.

P5.6.6 RMP Part VI: Summary of Activities in the Risk Management Plan by Medicinal Product

The summary must include key elements of the RMP with a specific focus on risk minimisation activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information.
P5.6.7 RMP Part VII: Annexes to the Risk Management

The RMP should contain the annexes listed below.

RMP annex 1: Current local package insert
RMP annex 2: Worldwide product registration/marketing authorisation status by country
RMP annex 3: Synopsis of on-going and completed clinical trial programme
RMP annex 4: Synopsis of on-going and completed pharmaco-epidemiological study programme
RMP annex 5: Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP Part III
RMP annex 6: Specific adverse event follow-up forms
RMP annex 7: Protocols for proposed and on-going studies in RMP Part IV
RMP annex 8: Synopsis of newly available study reports for RMP Parts III-IV
RMP annex 9: Details of proposed additional risk minimisation activities (if applicable)
RMP annex 10: Mock up examples in English or Malay/Bahasa Malaysia of the material provided to healthcare professionals and patients as part of conditions for registration.
RMP annex 11: Other supporting data (including referenced material)
PART 6: PHARMACOVIGILANCE SYSTEM MASTER FILE
Under development

PART 7: PHARMACOVIGILANCE AUDIT AND INSPECTION
Under development
PART 8

MISCELLANEOUS
PART 8: MISCELLANEOUS

P8.1 Safety Communication

Communication tools and channels have become more numerous and varied over time, offering the public more information than was previously possible. The use of this increasing variety of means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations.

P8.1.1 Direct Healthcare Professional Communication (DHPC)

A Direct Healthcare Professional Communication (DHPC) is defined in this document as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by PRH or the Authority (in special cases), to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimisation activities.

The PRH must ensure that it has an appropriate system of pharmacovigilance and risk management to assure responsibility and liability for marketed medicines, and to ensure appropriate action can be taken when necessary.

Situations where a Direct Healthcare Professional Communication should be considered as part of the risk-management process include: suspension, withdrawal; revocation of a product registration with recall of the medicine from the market for safety reasons; important changes to the package insert (e.g. new warnings or contraindications, reduced recommended dose, or restricted indications or availability); or a change in the balance of benefits and risks for a medicine.

To distribute a DHPC in Malaysia, the PRH should submit a draft communication plan to the Authority for approval that includes:

i. Objective;
ii. Scheduled timeline proposed;
iii. Recipients;
iv. Dissemination method;
v. Current approved package insert with changes clearly marked/highlighted;
vi. Other related communications and post-communication strategy.

The appended (Appendix 7) Template for Direct Healthcare Professional Communication should be followed.
Further recommendations on DHPC:

- Safety information should be clear and concise; it should not exceed three (3) pages;
- The reason for dissemination should be explained (e.g. Availability of new data);
- Recommendations to healthcare professionals should be given on how to minimise risk, if known and information for the general public;
- The safety concern should be placed in the context of the overall benefit of treatment.

The distribution of a proposed package insert with highlighted changes should be informed and agreed with the Authority prior to circulation.

**P8.1.2 Consumer Medication Information Leaflet (RiMUP)**

Please refer to *Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna Edisi Kedua April 2014 (Semakan Mac 2015)* for further details.

**P8.2 Others**

**P8.2.1 Boxed Warning**

The concept of boxed warning is intended to highlight life-threatening or serious and/or unexpected adverse reactions. This shall be succinct and designed to draw prescriber's attention to detailed information within the main text of package insert.

There are two (2) types of boxed warnings:

a) **Black box warning**
   This must be separated and highlighted from the other text in the package insert, typically characterised by a black box border and normally placed in the first section of the package insert.

b) **Boxed warning**
   This is typically characterised by a black box border within the text in the package insert.

A boxed warning is ordinarily used to highlight the following situations to prescribers:

i. There is an adverse reaction so serious compared to the potential benefit from the drug (e.g. fatal, life-threatening, or permanently disabling) whereby it is essential that the adverse reaction be considered in assessing the risks and benefits of using the drug.

ii. There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug such as:

   a) Patient selection;
   b) Careful monitoring;
c) Avoiding certain concomitant therapy;
d) Addition of another drug;
e) Managing patients in a specific manner;
f) Avoiding use in a specific clinical situation.

iii. Drug approval within restrictions to ensure safe use because it is concluded that the drug can be safely used only if distribution or use is restricted.

iv. Certain especially important information, e.g. under Warnings and Precautions and Contraindications sections.

v. In some cases, a boxed warning may be based on expected/anticipated adverse reactions, though normally based on observed serious adverse reactions.

vi. Drug has important risk/benefit information that is unique/specific to that drug only in its drug class.

vii. Serious or life-threatening drug interactions.

The information provides a brief, concise summary of the information that is critical for prescriber to be aware of, including any restriction on distribution or use. If there is more detailed discussion of the concerned matter in either Contraindications or Warnings and Precautions section or in any other labelling section that contains pertinent information, a cross reference to that section must be provided (e.g. see Warnings and Precautions).

There may be a valid reason for the use of boxed warning on the package insert and it will be discussed on a case-by-case basis and the recommendations for boxed warning will be in-line with other regulatory agencies.
ASSOCIATED DOCUMENTS
APPENDIX 1

REPORT ON SUSPECTED ADVERSE DRUG REACTIONS
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING

(Please report all suspected adverse drug reactions including those for vaccines, cosmetics and traditional products. Do not hesitate to report if some details are not known. Mandatory fields are marked with *, but please give as much other information as you can. Identifiers of Reporter, Patient and Institution will remain Confidential.)

REPORT No. (for official use only):

PATIENT INFORMATION
- L.C. No. / R.N. / Initials
- *Age
- *Gender (please tick)
- Wt (kg)
- *Ethnic Group
- Signature (if applicable)
- Initial Report
- Follow-up Report

*ADVERSE REACTION DESCRIPTION (Inc. sequence of adverse events, details of medication, interactions)

- Time to onset of reaction:
- Date start of reaction:
- Date end of reaction:
- Reaction subsided after stopping drug / reducing dose: Yes/No/Unknown
- Reaction reappeared after reintroducing drug: Yes/No/Unknown
- Extent of reaction: Mild/Moderate/Severe
- Seriousness of reaction: Life-threatening/Caused or prolonged hospitalisation/Caused disability or incapacity/Caused birth defect
- Treatment of adverse reaction & action taken:

Outcome:
- Recovered fully
- Recovering
- Not recovered
- Unknown
- Fatal
- Date & Cause of death

Drug-Reaction Relationship: Certain/Probable/Possible/Unlikely/Unclassifiable

*Suspected Drug

<table>
<thead>
<tr>
<th>Product / Generic Name</th>
<th>Dose &amp; Frequency Given</th>
<th>MAL and Batch No.</th>
<th>Therapy Dates</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Start</td>
<td>Stop</td>
</tr>
</tbody>
</table>

Concomitant Drug (please state "Nil" if none):

<table>
<thead>
<tr>
<th>Product / Generic Name</th>
<th>Dose &amp; Frequency Given</th>
<th>MAL and Batch No.</th>
<th>Therapy Dates</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Start</td>
<td>Stop</td>
</tr>
</tbody>
</table>

(Please attach additional sheets if necessary)

Relevant Investigations / Laboratory Data

Relevant Medical History (e.g. hepatic/renal dysfunction, allergies, pregnancy status, etc)

Reporter Details
- *Name
- *Institution Name
- Address:
- Designation:
- *Tel No.
- Email Address:
- Date of Report:
- Signature:

Submission of a report does not constitute an admission that medical personnel or the products caused or contributed to the reaction. Thank you for reporting.
**Consumer Side Effect Reporting Form**

**National Centre for Adverse Drug Reactions Monitoring**

*Help us make medicines safer*

Please fill in all sections marked with * and give as much other information as you can.

All personal data will remain confidential.

### Information about the person who had the side effect

<table>
<thead>
<tr>
<th>Name:</th>
<th>Nationality:</th>
<th>Male</th>
<th>Female</th>
<th>Date of report:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malaysian</td>
<td></td>
<td></td>
<td>Reporter's name:</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
<td></td>
<td>Tel. Number:</td>
</tr>
<tr>
<td><em>Gender</em>:</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td>Email address:</td>
</tr>
<tr>
<td><em>Ethnicity</em>:</td>
<td>Malay</td>
<td>Chinese</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Age</em>:</td>
<td></td>
<td>Indian</td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

*Any health problems / allergies / pregnancy? (please specify):*

E.g., diabetes, high blood pressure, asthma, allergy to penicillin, or is pregnant.

### Information about the medication(s) suspected to cause the side effect, and other medications

<table>
<thead>
<tr>
<th>Suspected Medicine(s): (please attach additional sheets if necessary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected medicine name (include M/N number if known)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
</tbody>
</table>

*Were any other medicines taken at the same time?:*  
☐ Yes (please give the details below)  ☐ No

| Other medicine(s) name (include M/N number if known) | Dosage (e.g., 250mg three times daily) | Dates: Started | Dates: Stopped | Reason for use |
|---------------------------------------------------------------|

### Information on the side effect(s)

1. *Date of side effect:*  
   a) Reaction started on [ ] [ ] [ ]  
   b) Reaction subsided on [ ] [ ] [ ]

2. *Please describe the side effect(s) experienced:*

3. *How long was the medication(s) taken before the side effect appeared?* [ ] minutes/hours/days/months/years (choose)

4. *Did the side effect subside when the medication(s) was stopped?*  
   ☐ Yes  ☐ No  ☐ Did not stop taking the medicine

5. *Did the side effect reappear when the medication(s) was taken again?*  
   ☐ Yes  ☐ No  ☐ Did not take again

6. *How serious was the side effect? (select all that apply below)*  
   ☐ Mild or slightly uncomfortable  ☐ Had to seek medical advice  ☐ Admitted to the hospital
   ☐ Uncomfortable but could carry out daily activities  ☐ Bad, interferes with daily activities  ☐ Other: [ ]

7. *Was any treatment given/medication taken to overcome the side effect?*  
   ☐ Yes (please specify)  ☐ No

8. *What is the current outcome of the side effect?*  
   ☐ Fully recovered  ☐ Getting better  ☐ Side effects continuing  ☐ Caused death

Thank you for reporting.
BORANG PENGANTARAN KESAN SAMPINGAN RINGAN SELEPAS PELAIAN

Pada kebanyakan waktunya, kesan sampingan tidak menyebabkan kesan serius. Walaupun begitu, kesihatan anda atau orang yang berada di berhawa juga anda mestilah memahami kesan sampingan yang mungkin terjadi seketika serta boleh mengambil tindakan kesehatan semasa atau setelah sambungan vaksin diterima.

Nama klinik/sekolah/ lain-lain tempat dimana vaksin diterima: ..................................................

1. Maklumat Penerima Vaksin:

a) Name: ........................................................................

e) No. Tel: ........................................................................

b) Umur: ......................... c) Jenis: lelaki f) Bangsa: Melayu i) Lain-lain, nyatakan: .............................................

Perempuan Cina

Lain-lain, nyatakan: .............................................

d) Alamat rumah: .............................................................

3. Bahagian badan dimana vaksin disuntik: .................................................................

4. Kesalahan yang dialami:

(Tempoh masa diantara vaksin diterima dan kesan sampingan berlaku adalah penting untuk diisi)

<table>
<thead>
<tr>
<th>Kesaran sampingan</th>
<th>Tandakan v jika berkaitan</th>
<th>Tempoh masa diantara vaksin diterima dan kesan sampingan berlaku (*sotong yang tidak berkanan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Kesaran pada tempat suntikan:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Bengkak</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>ii) Salat</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>iii) Kegiatan</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>iv) Merah pada tempat suntikan</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>v) Lain-lain (nyatakan)</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>b. Darah</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>c. Kesaran alih/ruam/gatal*</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>d. Sakit otot/badan*</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>e. Lesu Badan</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>f. Sakit kepala</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>g. Pusing kecemas /iwa / muntah*</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
<tr>
<td>h. Lemah atau kah*</td>
<td>..........</td>
<td>mint/jam /hari /minggu*</td>
</tr>
<tr>
<td>i. Lain-lain (nyatakan)</td>
<td>..........</td>
<td>mint/jam /hari *</td>
</tr>
</tbody>
</table>

5. Adakah penerima vaksin nantinya sebarang rawatan di klinik/hospital untuk kesan sampingan yang dialami?

Ya Tidak

6. Adakah kesan sampingan tersebut dapat diatasi atau pulih? : Ya Tidak

Seluruh kesaran yang disebutkan adalah sulit dan hanya akan digunakan untuk tujuan memantau kesan sampingan selepas pelayan sebahagia

Untuk Diisi Kakitangan Kesihatan:

i. Maklumat vaksin digunakan:

   a) Jenis vaksin: ........................................................................

   b) Jenama vaksin: ........................................................................

   c) No. kelompok : .........

   d) Dose vaksin: ........................................................................

   e) Umur: ........................................................................

   f) Jenis vaksin: ........................................................................

   g) No. telefon: ........................................................................

   h) No. kumpulan : ........................................................................

   i) No. telefon: ........................................................................

ii. Maklumat Kakitangan Kesihatan yang Memberi Vaksin:

   a) Name: ........................................................................

   b) Cop/Alamat tempat berjaga: .............................................

   c) No. telefon: ........................................................................

   d) Tariikh laporan: ........................................................................

Jika kesan sampingan yang serius, agasida kesihatan perlu mengisi Borang Pelaporan Kesaran Adverse Ubat dan merujuk kepada Gerepatan Perdagangan Perkhidmatan Kesihatan Vaksin di Malaysia.

Sila majukan borang yang terdahulu dan sebarang pertanyaan atau aduan ke Biro Pengawalan Farmaseutikal Ketegangan di talian 03-7883400 atau FAX 03-77381238.
<table>
<thead>
<tr>
<th>CIOMS FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSPECT ADVERSE REACTION REPORT</td>
</tr>
</tbody>
</table>

**I. REACTION INFORMATION**

<table>
<thead>
<tr>
<th>1. PATIENT INITIALS</th>
<th>2. DATE OF BIRTH</th>
<th>3. AGE</th>
<th>4.4 REACTION ONSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>(First, last)</td>
<td>Day</td>
<td>Month</td>
<td>Year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION:
- [ ] PATIENT DIED
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- [ ] INVOLVED
- [ ] PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE-ThREATENING

**II. SUSPECT DRUG(S) INFORMATION**

<table>
<thead>
<tr>
<th>14. SUSPECT DRUG(S) (Include generic name)</th>
</tr>
</thead>
</table>

20. DID REACTION ANGATE AFTER STOPPING DRUG?
- [ ] YES
- [ ] NO
- [ ] NA

<table>
<thead>
<tr>
<th>15. DAILY DOSES(S)</th>
<th>16. ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
</table>

21. DID REACTION REAPPEAR AFTER REINTRODUCITION?
- [ ] YES
- [ ] NO
- [ ] NA

<table>
<thead>
<tr>
<th>17. INDICATION(S) FOR USE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>18. THERAPY DATES (From/to)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>19. THERAPY DURATION</th>
</tr>
</thead>
</table>

**III. CONCOMITANT DRUG(S) AND HISTORY**

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (Exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc)

**IV. MANUFACTURER INFORMATION**

<table>
<thead>
<tr>
<th>24a. NAME AND ADDRESS OF MANUFACTURER</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>24b. MFR CONTROL NO.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>24c. DATE RECEIVED BY MANUFACTURER</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>24d. REPORT SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY</td>
</tr>
<tr>
<td>LITERATURE</td>
</tr>
<tr>
<td>HEALTH PROFESSIONAL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24e. DATE OF THIS REPORT</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>25a. REPORT TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>INITIAL</td>
</tr>
<tr>
<td>FOLLOWUP</td>
</tr>
</tbody>
</table>
APPENDIX 2: SUMMARY OF EXPEDITED ADR REPORTING REQUIREMENTS TO THE AUTHORITY (TIMELINE FOR ADR REPORTING)

<table>
<thead>
<tr>
<th>Reporter Category</th>
<th>Types of Adverse Reaction</th>
<th>Time Frame for Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare Professional</td>
<td>Serious with fatal or life-threatening outcome</td>
<td>As soon as possible, but no later than 7 calendar days, after first knowledge of the case. This report should include the assessment from the investigation and other relevant document.</td>
</tr>
<tr>
<td></td>
<td>Serious but there are no life-threatening or fatal outcome</td>
<td>As soon as possible but no later than 15 calendar days after first knowledge of the case.</td>
</tr>
<tr>
<td></td>
<td>Non-serious</td>
<td>As soon as possible after first knowledge of the case.</td>
</tr>
<tr>
<td>Product Registration Holder</td>
<td>Local report</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serious (expected or unexpected) with fatal or life-threatening outcome</td>
<td>As soon as possible, but no later than 7 calendar days, after first knowledge by PRH, followed by complete report within 8 calendar days. This report should include the assessment from the investigation and other relevant document.</td>
</tr>
<tr>
<td></td>
<td>Serious, expected or unexpected but there are no life-threatening or fatal outcome</td>
<td>As soon as possible but no later than 15 calendar days after first knowledge by registration holder</td>
</tr>
<tr>
<td></td>
<td>Non-serious, expected or unexpected</td>
<td>Within 30 calendar days</td>
</tr>
<tr>
<td>Foreign reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individual case report</td>
<td>Not required on routine basis</td>
</tr>
<tr>
<td></td>
<td>Notification of any significant safety issue such as new information impacting on risk(s) benefit profile of medicinal product including international regulatory decision or action</td>
<td>No later than 3 calendar days</td>
</tr>
<tr>
<td></td>
<td>Withdrawal/suspension of registration in any country</td>
<td>24 hours after first knowledge by registration holder</td>
</tr>
</tbody>
</table>
APPENDIX 3: PRH ADR SUMMARY REPORT FORMAT

The information included in the annual summary report will vary depending on the adverse reaction cases reported. Lack of significant new information should be mentioned for each section.

The Authority expects that the annual summary report will contain the following:

- Introduction
- Changes to the PRH’s product safety information
- Significant regulatory actions bearing on safety (domestic and foreign)
- Line listing(s) and summary tabulations (see below)
- Critical Analysis:
  - A change in characteristics of expected reactions, e.g. severity, outcome, target population
  - Serious unexpected reactions, placing into perspective the cumulative reports since marketing
  - Non-serious unexpected reactions
  - An increased reporting frequency of expected reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence
  - Comparative analysis of reporting rates using patient exposure estimate (analyses may be done in the context of amount of sales of the drug or by estimating the number of patient days of exposure)
  - The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):
    - drug interactions
    - experience with overdose, deliberate or accidental, and its treatment
    - drug abuse or misuse
    - positive or negative experiences during pregnancy or lactation
    - experience in special patient groups (e.g. children, elderly, organ impaired)
    - effects of long-term treatment
- Other information (e.g. information related to effectiveness and late-breaking information)
- Conclusion

Line Listing(s) and Summary Tabulations

The Authority expects that the following types of cases will be included in the line-listing and that attempts will be made to avoid duplicate reporting of cases from the literature and regulatory sources:
• For drugs, from unsolicited sources (see Section P3.6.1):
  o All domestic, serious ADRs
  o All domestic non-serious unexpected ADRs
• Domestic cases of unusual failure in efficacy
• For drugs, from solicited sources where there is a reasonable possibility that the drug caused the adverse reaction (see Section P3.6.2):

Presentation of the Line Listing

The line listing(s) should include each patient only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organised (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

• PRH case reference number
• Source of report (e.g. clinical trial, literature, spontaneous, regulatory authority)
• Age and gender
• Daily dose of suspected health product (and, when relevant, dosage form or route)
• Date of onset of the reaction
• Dates of treatment
• Description of reaction (International standard terminology is recommended, e.g. MedDRA, WHO-ART, SNOMED-CT)
• Patient outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown).
• Comments, if relevant (e.g. causality assessment if the PRH disagrees with the reporter; concomitant health products suspected to play a role in the reactions directly or by interaction; indication treated with suspect health product(s); dechallenge/rechallenge results if available).

Summary Tabulations

An aggregate summary for each of the line listings should be presented. These tabulations ordinarily contain more terms than patients do. It is useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for expected and unexpected reactions; other breakdowns might also be appropriate (e.g. by source of report). When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description, rather than a formal table, is considered suitable.
APPENDIX 4: EXAMPLES OF SUMMARY TABULATION

Note: PRHs can modify these examples to suit specific situations, as appropriate.

Table 1: Estimated Cumulative Subject Exposure from Clinical Trials

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal product</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex*

<table>
<thead>
<tr>
<th>Age range</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data from completed trials as of [date]

Table 3: Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group

<table>
<thead>
<tr>
<th>Racial Group</th>
<th>No. of Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Cumulative Exposure from Marketing Experience*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Sex</th>
<th>Age(years)</th>
<th>Dose (mg/day)</th>
<th>Formulation</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>12-18</td>
<td>18-60</td>
<td>&gt;60</td>
<td>&lt;40</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes cumulative data obtained from month/day/year through month/day/year
Table 5: Interval Exposure from Marketing Experiences

<table>
<thead>
<tr>
<th>Indication</th>
<th>Sex</th>
<th>Age(years)</th>
<th>Dose (mg/day)</th>
<th>Formulation</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>12-18</td>
<td>18-60</td>
<td>&gt;60</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>-</td>
<td>&lt;40</td>
<td>&gt;40</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Includes cumulative data obtained from month/day/year through month/day/year

Table 6: Cumulative Tabulations of Serious Adverse Events from Clinical Trial

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Investigational Medicinal Product</th>
<th>Blinded</th>
<th>Active Comparator</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous Disorder</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Numbers of Adverse Drug Reactions by Term from Post-Marketing Sources

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous, including Authority and literature</th>
<th>Non-interventional post-marketing study and reports from solicited sources*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>Interval</td>
<td>Cumulative</td>
</tr>
<tr>
<td>SOC 1</td>
<td>MedDRA PT</td>
<td>MedDRA PT</td>
</tr>
</tbody>
</table>

*This does not include interventional clinical trials
**APPENDIX 5: Examples of Summary of Safety Signals That Were Ongoing or Closed During the Reporting Interval**

<table>
<thead>
<tr>
<th>Signal term</th>
<th>Date detected</th>
<th>Status (ongoing or closed)</th>
<th>Date closed (for closed signals)</th>
<th>Source of signal</th>
<th>Reason for evaluation &amp; summary of key data</th>
<th>Method of signal evaluation</th>
<th>Action(s) taken or planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>month/year</td>
<td>Ongoing</td>
<td>Month/year</td>
<td>Meta-analysis (published trials)</td>
<td>Statistically significant increase in frequency</td>
<td>Review meta-analysis and available data</td>
<td>Pending</td>
</tr>
<tr>
<td>TEN</td>
<td>month/year</td>
<td>Closed</td>
<td>Month/year</td>
<td>Spontaneous report</td>
<td>Rash already an identified risk. SJS not reported in pre authorisation CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset.</td>
<td>Targeted follow up of reports with site visit to one hospital. Full review of cases by PRH dermatologist and literature searches.</td>
<td>RSI updated with a Warning and Precaution. DHPC sent to oncologists. Effectiveness Survey planned 6 months post DHPC. RMP Updated.</td>
</tr>
</tbody>
</table>

**Explanatory notes**

**Signal term**
A brief descriptive name of a medical concept for the signal. The description may evolve and be refined as the signal is evaluated. The concept and scope may, or may not, be limited to specific MedDRA term(s), depending on the source of signal.

**Date detected (month/year)**
Month and year the PRH became aware of the signal.

**Status**
- **Ongoing**: Signal under evaluation at the DLP of the PBRER. Provide anticipated completion date, if known.
- **Closed**: Signal for which evaluation was completed before the DLP of the PBRER.

**Note**: A new signal of which the PRH became aware during the reporting interval may be classified as closed or ongoing, depending on the status of signal evaluation at the DLP of the PBRER.

**Date closed (month/year)**
Month and year when the signal evaluation was completed.
**Source of signal**
Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous adverse event reports, clinical trial data, scientific literature, non-clinical study results, or information requests or inquiries from a regulatory authority.

**Reason for evaluation**
A brief summary of key data and rationale for further evaluation.

**Actions taken or planned**
State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the DLP, these should be listed. Otherwise leave blank for ongoing signals.
APPENDIX 6 MAPPING SIGNAL AND RISKS EVALUATION TO PBRER SECTION

Safety data from available information sources

 Previously recognised risk?

 N

 Previously recognised risk?

 Y

 New information constituting signal?

 N

 Safety signal detected?

 N

 No further documentation in PBRER

 Y

 Safety signal – Section 15

 Safety signal ongoing Section 15

 Close?

 N

 Section 16.2

 Refuted Signal

 Potential or Identified Risk

 Important?

 N

 Section 16.4

 Key to benefit evaluation?

 N

 Section 18.2

 Action(s) proposed

 Y

 No further documentation in PBRER

 Y

 Consider to update relevant document

 Section 19
APPENDIX 7: TEMPLATE FOR DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

<Product Holder Details>
<Date>

Direct Healthcare Professional Communication:
Product Name® (active ingredient) [MAL number]:
<Safety issue>

Dear Healthcare Professional,

<Brief statement>

Summary

- Point 1
- Point 2
- Point 3

<Note: The Summary Section should be in larger font size than the other section of the DHPC>

The communication of this information has been agreed with the National Centre for Adverse Drug Reaction Monitoring, National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia.

Indications approved in Malaysia

<State the indications as approved>

Further information on the safety concern

<Details on the safety issue; i.e. trial involved, risk minimisation measures>

Status for product information

<Include changes/updates for the current package insert>
Call for adverse event reporting

To make a report, kindly contact the National Centre for Adverse Drug Reaction Monitoring, National Pharmaceutical Regulatory Agency (NPRA):

- By phone: 03-78835400 (Ext: 8460/8466)
- Or mail to the following address:
  National Pharmaceutical Regulatory Agency (NPRA)
  Lot 36, Jalan Universiti
  46200 Petaling Jaya
  Selangor, Malaysia

Adverse drug reactions should also be reported to <Product Registration Holder (Malaysia) Sdn Bhd>, <Name of Person In-charge> at +6012-1234567 or +603-98765432.

For further medical information on <Product Name®>, please contact <Product Registration Holder (Malaysia) Sdn Bhd> medical contact, <Physician Name> contactable at +6012-3456789.

Yours sincerely,

(Name of Safety Person In-charge)

Designation

Reference

<Any literature references/scientific information sourced>