MALAYSIAN GUIDELINES ON GOOD PHARMACOVIGILANCE PRACTICES (GVP) FOR PRODUCT REGISTRATION HOLDERS

First Edition, August 2021

National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

Ministry of Health, Malaysia

This guideline is issued by the Senior Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984. NPRA reserves the right to amend any part of the guideline whenever it deems fit.

This reference guide serves as a guidance for the product registration holders to establish pharmacovigilance system within their organisation framework.

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RECORD OF UPDATES ON PHARMACOVIGILANCE RELATED GUIDELINES ISSUED BY NPRA

Date	Name and Version	Summary of the Edition/Changes
March 2002	Malaysian Guidelines for the Reporting & Monitoring	This is the first guideline that was developed to outline the requirements and procedures to be followed for **the submission of adverse drug reactions (ADR) reports** to the Drug Control Authority (DCA). This guideline is intended for both healthcare professionals (HCPs) and product registration holders (PRHs).
September 2016	Malaysian Pharmacovigilance Guidelines Second Edition 2016	This edition incorporates the requirements and procedures for **the submission of ADR reports as well as submission of other information regarding product safety by PRHs to the DCA [e.g. Risk Management Plan (RMP), Periodic Benefit-Risk Evaluation Report (PBRER)].** This guideline is intended for both HCPs and PRHs.
July 2021	Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders First Edition, July 2021	This guideline, which is intended for PRHs, outlines the requirements and procedures of Good Pharmacovigilance Practices (GVP) activities including but not limited to **the submission of ADR and adverse event following immunisation (AEFI) reports, and the submission of information regarding product safety** to the DCA. This guideline has also included **one (1) new part** (Part 6) related to **Pharmacovigilance System Master File.** The chapter on “Submission of ADR Reports by Healthcare Professionals” has been taken out and issued as a separate guidance.

PREAMBLE

Pharmacovigilance is defined by the World Health Organisation (WHO) as the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems. Essentially, it is about drug safety and the ultimate goal of pharmacovigilance is to accurately determine and optimise the benefit-risk ratio of a drug product throughout its life cycle.

Malaysia set up its national pharmacovigilance system with the establishment of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) in 1987. MADRAC acts as an advisory body to the Drug Control Authority (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 WHO Programme for International Drug Safety Monitoring since 1990.

One of the pharmacovigilance requirements for pharmaceutical companies is the establishment of a pharmacovigilance system within their organisations. Pharmaceutical companies need to ensure their pharmacovigilance systems are up to standards as any deficiencies may impact patient safety. In view of this necessity, this guideline has been developed to assist and provide guidance to pharmaceutical companies to establish good pharmacovigilance systems within their organisations. This guideline outlines responsibilities and requirements for all pharmacovigilance activities such as Adverse Drug Reaction (ADR) /Adverse Effects Following Immunisation (AEFI) Reports Management, Risk Management Plan (RMP) and Periodic Benefit-Risk Evaluation Report (PBRER). The goal of this guideline is to facilitate the PRHs in carrying out their pharmacovigilance responsibilities and ultimately enhance the efforts of ensuring product safety in Malaysia. For this, one (1) new part related to Pharmacovigilance System Master File has been included in this guideline.

This guideline is mainly adopted from the European Good Pharmacovigilance Practices and other GVP-related guidelines by other regulatory agencies were also referenced. Nevertheless, the adoption of those guidelines does not undermine the right of NPRA to impose additional or different requirements to suite local pharmacovigilance scenarios. Accordingly, the stakeholders have been closely engaged in the process of drafting the guideline. Stakeholders' consultation was formally performed on the Unified Public Consultation (UPC) platform of the Malaysia Productivity Corporation in December 2020.

This reference guide serves as a guidance for the product registration holder to establish pharmacovigilance system within their organisation framework.

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GLOSSARY

Active ingredient
Interchangeable with active substance.

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.

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 the 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*

Biologics
Biologic/Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnological methods and other cutting-edge technologies. This product imitates the natural biological substances in our bodies such as hormones, enzymes or antibodies [please refer to the current Drug Registration Guidance Document (DRGD)].

Biosimilars
A new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well-established, medicinal product [please refer to the current Drug Registration Guidance Document (DRGD)].

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 countries.

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 PRH 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 CCDS prepared by the PRH and which PRH requires to be listed in all countries where the company markets the product, except when the 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 Maklumat Ubat Untuk Pengguna* (RiMUP)
A leaflet containing information for the consumers 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 PRH or by the 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.

Inspection
The act by an authority(s) conducting an official review of documents, facilities, records and any other resources that are deemed by the authority(s) to be related to the pharmacovigilance system.

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, which are not in accordance with the registered information.

New Drug Product
New Drug Product (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the Control of Drug and Cosmetic Regulation (CDCR) 1984. This includes New Chemical Entity and hybrid [please refer to the current Drug Registration Guidance Document (DRGD)].

Newly identified signal
In PBRER, 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.

Non-serious AEFI
An event that is not ‘serious’ and does not pose a potential risk to the health of the recipient. Non-serious AEFIs should be carefully monitored because they may signal a potentially larger problem with the vaccine or immunisation, or have an impact on the acceptability of immunisation in general.

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 PBRER, a signal that remains under evaluation at the data lock point. *See also Signal, Data lock point.*

Orphan medicine
A medicinal product that is primarily intended to treat, prevent or diagnose a rare disease. Rare disease refers to a life-threatening or chronically debilitating rare condition as listed in the Malaysian Rare Disease List.

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 PRH at defined time points after the approval of registration.

Pharmacovigilance (PV)
Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Pharmacovigilance system
A system used by the PRH 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 registered medicinal products and detect any change to their benefit-risk balance.

Pharmacovigilance System Master File (PSMF)
A detailed description of the pharmacovigilance system used by the PRH with respect to one or more registered medicinal products.

Pharmacovigilance System Summary (PVSS)
A document that briefly describes or summarises the pharmacovigilance system of the PRH.

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

Product information
Documents providing officially approved information on a medicine which are intended for healthcare professionals and patients on a medicine. The product information includes the package insert, RiMUP and labelling.

Reference safety information
In PBRER for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the PRH.

It is a subset of information contained within the PRH‘s reference product information for the PBRER. 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 to patients‘ health or public health and any risk of undesirable effects to the environment.

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

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 a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verification 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 is therefore 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.

Special Interest
An event of special interest (serious or non-serious) is one of scientific and medical concern specific to particular drug which need an ongoing monitoring and communicated rapidly.

Spontaneous report, synonym: spontaneous notification
An unsolicited communication by a healthcare professional or consumer to a PRH 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 registered 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 for which the signal validation process has verified that the available documentation contains sufficient evidence in 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

ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunisation
CCDS	Company Core Data Sheet
CIOMS	Council for International Organisation of Medical Sciences
DCA	Drug Control Authority
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
DRGD	Drug Registration Guidance Document
IBD	International Birth Date
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
IRSR	Issue-related Summary Report
MedDRA	Medical Dictionary for Regulatory Activities
NPRA	National Pharmaceutical Regulatory Agency
OTC	Over-The-Counter
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Package Insert
PRH	Product Registration Holder
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVSS	Pharmacovigilance System Summary
RiMUP	*Risalah Maklumat Ubat untuk Pengguna*
RMP	Risk Management Plan
RPPV	Responsible Person for Pharmacovigilance
RSI	Reference Safety Information

SAE Serious Adverse Event

SOC System Organ Class

TMHS Traditional Medicines and Health Supplements

WHO World Health Organisation

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PART 1:

General Information on Pharmacovigilance

PART 1: GENERAL INFORMATION ON 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.

The National Adverse Drug Reaction (ADR) Monitoring Centre, National Pharmaceutical Regulatory Agency (NPRA) is responsible for product safety monitoring including ADR/Adverse Event Following Immunisation (AEFI) Reporting.

P1.1 INTRODUCTION TO 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, particularly 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.

P1.1.2 Scope of Pharmacovigilance in Malaysia

The scope of pharmacovigilance in Malaysia includes (but is not limited to):

i. ADR/AEFI reporting by healthcare professionals, consumers and PRH, collection of reports and monitoring by PRH and the Authority.

ii. Safety profile monitoring through signal management process, as well as preparation and evaluation of Periodic Benefit-Risk Evaluation Report (PBRER) and Risk Management Plan (RMP).

iii. 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.

iv. Safety communication, for example Direct Healthcare Professional Communication (DHPC) Letter, Package Insert (PI), websites, publications and Consumer Medication Information Leaflet (RiMUP); to ensure product information is updated with latest safety information according to NPRA directives and circulars.

P1.2 LEGAL BASIS

i. The legal basis of this guideline can be found in the Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment in 2006),

a) Regulation 28: Reporting adverse reactions - 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.

b) Regulation 29:

(1) The Director of Pharmaceutical Services may issue written directives or guidelines to any person or a group of persons as he or she deems necessary for the better carrying out of the provisions of these Regulations and which in particular relate to— (a) product quality, safety and efficacy; (b) labelling; (c) change of particulars of a product; (d) transfer of licences; (e) manufacturing; (f) storage includes requirements as to containers; (g) retailing; (h) promotion of sale including product information; (i) product recall; (j) product disposal; (k) the cost of product recall or product disposal; (l) clinical trials; or (m) records and statistics pertaining to manufacture, sale, supply, import or export of any products.

(2) Any person who contravenes any directives or guidelines issued by the Director of Pharmaceutical Services under subregulation (1) commits an offence.

ii. All 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 requirements e.g. directives, registration condition etc. issued by the Authority.

iv. This guideline should be read along with Drug Registration Guidance Document (DRGD) and any guidelines stated in the DRGD.

P1.3 CONFIDENTIALITY

The Authority will maintain strict confidentiality with regards to the identity of patients and reporters, which is align with the Personal Data Protection Act 2010.

P1.4 REPORTING OF ADVERSE DRUG REACTION (ADR) AND ADVERSE EVENT FOLLOWING IMMUNISATION (AEFI)

i. Reporting of ADR and AEFI are the main activities in pharmacovigilance, so as to improve the safety profile of the medicinal products. The National ADR Monitoring Centre, 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/AEFI reporting schemes, in combination with clinical and epidemiological studies as well as literature, are used to aid in the decision-making on product safety. Information from all these sources may lead to the following regulatory changes/actions:

a) Restriction in usage;

b) Refinement of dosage instructions;

c) Strengthening of specific warnings;

d) Reviewing of specific labelling requirements;

e) Changes in product information based on new findings;

iii. All reports submitted to NPRA are treated as confidential and reporters are not required to divulge the identity of the patient(s) involved.

P1.4.1 Scope of ADR Reporting

i. The WHO encourages reporting of ALL suspected ADRs. Healthcare provider, PRH and consumer are requested to report ADRs suspected to be related to all products registered with the Drug Control Authority (DCA), e.g. pharmaceutical products including biologics, over–the-counter (OTC) products, health supplements, and natural products, even for common/minor or well-documented reaction.

ii. A reaction is suspected if the reporting healthcare professional, PRH or any person who possesses 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. All adverse reactions should be considered reportable according to the requirements outlined in this guideline regardless of whether or not the product was used in accordance with the product information provided by the PRH.

iv. 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.

v. As for regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it should meet the definition of an adverse drug reaction.

vi. In ADR reporting, priority should be given in the following categories:

a) 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;
- Is a medically important event or reaction.

Note: Medical and scientific judgement should be exercised in deciding whether or not expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered as serious.

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 drug dependency or drug abuse.

b) Unexpected/unlabelled ADRs for all new and generic products.

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

d) ADR(s) related to any suspected forms of drug interactions e.g. drug-drug, drug-food interactions, etc.

e) Change in frequency of a known ADR(s).

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

P1.4.2 Scope of AEFI Reporting

i. An AEFI is 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.

ii. Monitoring of AEFI is an effective way to monitor immunisation safety and contributes to the credibility of National Immunisation Programme (NIP).

iii. All AEFI should be reported.

a) Non-serious AEFI – An AEFI that is not 'serious' and does not pose a potential risk to the health of the recipient.

b) Serious AEFI – An event that either 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 defects. Any medical event that requires intervention to prevent one of the outcomes listed above may also considered as serious.

iv. There are five categories of AEFIs as listed in Table 1 below:

Table 1: Cause-specific categorisation of AEFI

No.	Cause-specific categorisation of AEFI	Definition
1	Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
2	Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.

3	Immunisation error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
4	Immunisation anxiety-related reaction	An AEFI arising from anxiety that developed from the anticipation of the immunisation.
5	Coincidental event	An AEFI that is caused by something other than the vaccine product, immunisation error or immunisation anxiety.

P1.5 OBJECTIVES OF ADR/AEFI MONITORING

The primary objectives of ADR/AEFI monitoring are as follows:

i. To detect ADR/AEFIs 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 or induce or influence the development, severity and incidence of adverse reactions e.g. genetic or racial factors, drug interactions, underlying conditions; and

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

P1.6 IMPACT OF ADR/AEFI MONITORING

P1.6.1 Analysis and the Possible Outcomes of ADR/AEFI Reports

When an ADR/AEFI report is analysed at the National ADR Monitoring Centre, NPRA, one of the following outcomes may be found:

i. The drug and the event were probably 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.

P1.6.2 Achievement of the Primary Objectives

The primary objectives (See Section P1.5) 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 ADR/AEFIs 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 Holder (PRH)

a) Initiate steps to make changes to the product dossier or product information leaflets or product 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/AEFI monitoring will also allow healthcare professional to rationally prescribe medicinal products including vaccine, whilst the public will be able to use medicinal products in an appropriate manner.

P1.7 GENERAL PRINCIPLES OF ADR/AEFI SUBMISSION

P1.7.1 ADR/AEFI Reporting Forms

The following are ADR/AEFI reporting forms available in Malaysia. The related forms can be found in (Appendix 1)

i. Online reporting form
- Available via https://npra.gov.my/index.php/en/health-professionals/reporting-adr.html

ii. Report on Suspected Adverse Drug Reactions
- Prepaid reporting blue form

iii. Consumer Side Effect Reporting Form (ConSERF)
- For the general public

iv. *Borang Pemantauan Kesan Advers Ringan Susulan Imunisasi*
- Specifically for parents or guardian or vaccinees for minor AEFI

v. Suspect Adverse Reaction Report Form (CIOMS Form I)
- For PRHs

P1.7.2 Content of ADR/AEFI Reports

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

a) A named suspected medicinal product;

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 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. However, for biologicals including biosimilars and vaccines, the specific brand name, product registration number, and batch number shall be provided for traceability purposes.

v. Standard medical terminology should be used to describe the ADR/AEFI. The use of vague terms should be avoided.

vi. The PRH may comment on the consideration of causal association between the suspected product(s) and reactions(s) reported and the PRH should provide the criteria by which he or she has made the assessment before submission of the report(s).

P1.7.3 Follow-Up Reports

i. Additional medically relevant information that was 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 generated 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 duplicated reports submitted to the Authority.

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

P1.8 ADR/AEFI REPORTING TIMELINE

Please refer to Appendix 2 for detailed information on ADR/AEFI reporting timeline.

P1.9 SUBMISSION OF PHARMACOVIGILANCE DOCUMENTS/ REPORTS

P1.9.1 ADR/AEFI Reporting Routes

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

i. Online reporting:
https://npra.gov.my/index.php/en/health-professionals/reporting-adr.html

ii. Post to:
The National Adverse Drug Reaction Monitoring Centre
National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia
Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz)
46200 Petaling Jaya
Selangor.

iii. Fax to:
603-79567075

iv. Email:
fv@npra.gov.my

P.1.9.2 Other Pharmacovigilance Documents Submissions Routes

Other pharmacovigilance documents can be submitted to the Authority via the following routes*:

i. Post to:
Pharmacovigilance Section
Centre of Compliance & Quality Control
National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia
Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz)
46200 Petaling Jaya
Selangor.

ii. Fax to:
603-79567075

iii. Email:
fv@npra.gov.my

*For PSMF, please submit in CD/USB flash drive and send to the Pharmacovigilance Section, Centre of Compliance & Quality Control, NPRA.

PART 2:

Pharmacovigilance System

PART 2: PHARMACOVIGILANCE SYSTEM

A pharmacovigilance system is a system used by the PRH to fulfil the pharmacovigilance tasks and responsibilities, and is designed to monitor the safety of registered medicinal products and detect any change to their benefit-risk balance.

P2.1 RESPONSIBILITIES OF THE PRODUCT REGISTRATION HOLDER (PRH)

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

P2.1.1 The Basic PV System

PV system should consist at least all of the following:

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

   a) A confirmation and/or reconciliation process should be undertaken during the transfer of ADR/AEFI report.

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

   a) A written procedure should adequately describe the way signal detection is performed, roles and responsibilities of personnel involved, as well as the source and method used for signal detection.

   b) There should be documentation and record for actions taken based on the outcome generated from the signal detection activities.

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

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

v. Action and communication with stakeholder(s) to protect public health (including but not limited to);

   a) Product information (label, package insert and RiMUP) should be kept up-to-date to ensure that there is no undue delay in updating documents. The product information should always tally with DCA directive and updated RSI unless justifiable;

   b) Fulfil registration requirement/condition and carry out any risk minimisation measure (e.g. special registration condition, RMP and regulatory action due to emerging safety issue).

vi. Pharmacovigilance audit

Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.

The audit strategy should cover all parts of the pharmacovigilance system including:

a) All pharmacovigilance processes and tasks;

b) The quality system for pharmacovigilance activities;

c) Interactions and interfaces with other departments, as appropriate;

d) Pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. PRH affiliates or third parties, such as contract organisations and other vendors);

e) Preparation of audit report and follow-up audits, including their dates and results.

vii. Training of the pharmacovigilance personnel:

a) Quality and adequacy of training, qualifications and experience of staff.

P2.1.2 Responsible Person for PV (RPPV) and Local Contact Person

i. As part of the pharmacovigilance system, PRH shall permanently and continuously at its disposal have an appropriately responsible person for PV activities. This person must have sufficient experience or training in all aspects of PV.

ii. The RPPV should preferably be based in Malaysia. However, in the event where the RPPV is based outside Malaysia (e.g. Singapore), the Authority would require a local contact person to be based in Malaysia. The local contact person must be contactable by the Authority at all times and should be able to contact the RPPV at all times to consult on any issues pertaining to PV. This local contact person must have experience or training in PV so that he or she understands his or her roles as the local contact person. If the RPPV or local contact person (if applicable) is not a healthcare professional, he or she should have access to a medically qualified person.

iii. The RPPV or local contact person (if applicable) shall act as the single PV contact point for the Authority, which is contactable whenever needed. The PRH should ensure there are back-up personnel for both RPPV and local contact person (if applicable) who are contactable whenever needed in the absence of the RPPV or local contact person (if applicable). The RPPV or local contact person (if applicable) should ensure that the back-up person has all the necessary information to fulfil the role.

iv. The PRH must provide the Authority with the details of the RPPV, local contact person (if applicable) and all back-up personnel (including full name, company's position, postal address, email address, telephone, hand phone number and fax numbers). Any changes of these details should promptly be informed to the Authority.

v. The roles of the RPPV are as follows (but not limited to):

a) To establish an effective system for monitoring ADR/AEFIs associated with the use of products registered under the PRH;

b) To ensure that information pertaining to ADR/AEFIs which come to the knowledge of the PRH, including through medical representatives, is collected and collated so that it is accessible at a single point;

c) To ensure that all local ADR/AEFI reports are submitted to the Authority in a timely manner (see Appendix 2);

d) To submit all relevant safety information such as PSUR/PBRER, post-registration study reports and RMP;

e) To ensure all risk minimisation plan (e.g. DHPC, patient guide and etc.) have been carried out;

f) 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;

g) To alert the Authority of any emerging safety issue(s) involving products registered under the PRH (see Section P8.1);

h) To ensure submission and management of PSMF is done accordingly as required by the Authority for the PRH under his or her responsibility.

vi. The RPPV may delegate specific tasks, under supervision, to appropriately qualified or trained individuals, provided that the RPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.

P2.1.3 Engagement of A Third Party on PV Activities

i. There are situations where the PRH may engage a third party on certain PV activities of the PV system, 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 guideline also applies to the other organisation or third party to which the tasks have been contracted to.

iii. When engaging a third party, the PRH shall draw up detailed and up-to-date contractual agreements or letter of appointment or official document. These should clearly document the contractual arrangements between the PRH and the other organisation, describing arrangements for delegation and the responsibilities of each party.

iv. In such relationships, it is very important that the contractual agreements or letter of appointment or official document specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities. Processes should be in place to avoid duplicate reporting to the Authority.

v. When transfer of pharmacovigilance data occurs between organisations that have set up contractual agreements or letter of appointment or official document, there should be a confirmation and/or reconciliation process to ensure that all notifications are received.

P2.1.4 Training of Personnel for Pharmacovigilance

i. Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel.

ii. All personnel involved in the pharmacovigilance activities shall receive initial and continued training. For PRH, this training shall relate to the roles and responsibilities of the personnel.

iii. The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel. Training plans should be based on training needs assessment and should be subject to monitoring.

iv. The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organisation should receive and be able to seek information about what to do if they become aware of a safety concern.

v. There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

vi. Adequate training should also be considered by the organisation for staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to activities related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

vii. Appropriate instructions on the processes to be used in case of urgency, including business continuity, shall be provided by the organisation to their personnel that involve in pharmacovigilance activities.

P2.2 SAFETY DOCUMENTS AND RECORD RETENTION

i. All pharmacovigilance data and documents relating to individual registered medicinal products must be retained for as long as the product registration exists and for at least an additional 10 years after the product registration has ceased to exist.

ii. The documents and records may be archived during retention period. However, the documents and records must be retrievable whenever requested by the Authority.

iii. For PRH transfer condition, the new PRH should ensure all PV data and record have been transferred fully from the existing PRH after DCA approval has been obtained for the transfer. In the context of stock depletion during the interim of the transfer, PRH who submit request to deplete the existing stock (the existing or new PRH) should be held responsible for the batches and quantity requested in the event of any pharmacovigilance issues or quality defects associated with those product batches. If the existing PRH is the one who submit the request and provide the information to the authority, the new PRH should also be provided with PV data and record of any pharmacovigilance issue and quality defect pertaining to the batches involved in the stock depletion (please refer to Appendix 2 for the submission timeline). Information pertaining to pharmacovigilance issues (such as emerging safety issue) which comes to the knowledge of the existing PRH should be submitted to the Authority or transfer to the new PRH for submission to the Authority. After ensuring all (including previous and transition period) PV data and record has been successfully transferred to the new PRH, the existing PRH may handle the PV data and record as per internal procedure.

PART 3:

Managing ADR/AEFI Reports

PART 3: MANAGING ADR/AEFI REPORTS

This part addresses the requirements for PRH with regards to data collection and reporting of all suspected ADR/AEFIs associated with medicinal products registered for human use in Malaysia.

Guidance regarding the reporting of suspected ADR/AEFIs occurring in special situations are also presented in this guideline (see Section P3.4).

P3.1 ADR REPORTING SYSTEM

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

P3.1.1 Key Personnel in Charge

The individual in charge of the ADR/AEFI reporting system should be qualified by pertinent training and experience relevant to their assigned responsibilities.

Requirements of the key personnel in charge of the ADR/AEFI reporting system:

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

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

iii. Responsible for ensuring completeness of the reports (see Section P3.2);

iv. Readily available to evaluate information related to potential ADR/AEFIs, to assess the seriousness, expectedness, and reportability of ADR/AEFIs;

v. Responsible to determine if an ADR/AEFI report qualifies for expedited reporting and if the report is to be included in the PBRER/Issue-Related Summary Report (IRSR).

P3.2 MANAGEMENT OF ADR/AEFI REPORTING

P3.2.1 Report Validation

Only valid ADR/AEFI reports qualify for reporting. All reports of suspected ADR/AEFIs should therefore be validated before reporting them to the Authority, to ensure they contain the minimum criteria as described in this guideline.

P3.2.1.1 One or More Identifiable Reporter (Primary Source)

i. The term 'identifiable' indicates that the organisation notified about the report has enough evidence of the existence of the person who reports the facts based on the available information.

ii. 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.

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

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

v. If information on the reporter's qualification is missing, the notification should be considered by default as a consumer report.

vi. To enable duplicate detection activities, all parties providing case information or approached for case information should be recorded in the ADR/AEFI report (not only the initial reporter).

vii. When the information is based on second-hand or hearsay, the report should be considered non-valid until it can be verified directly with the patient, the patient's healthcare professional or a reporter who had direct contact with the patient.

P3.2.1.2 One Single Identifiable Patient

i. The term 'identifiable' refers to the possibility of verification of the existence of a patient based on the available information.

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

iii. An ADR/AEFI report should not be considered valid for submission unless information is available for at least one of the patient qualifying descriptors as explained above. Furthermore, in the absence of a qualifying descriptor, a notification referring to a definite number of patients should not be regarded valid until an individual patient can be characterised by one of the qualifying descriptors for creating a valid ADR/AEFI report.

P3.2.1.3 One or More Suspected Substance/Medicinal Product

i. “Product” means:

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.

ii. Interacting substances or medicinal products should also be considered suspected.

P3.2.1.4 One or More Suspected Adverse Reaction

i. A valid report should contain at least one specific ADR/AEFI. The report does not qualify as a valid ADR/AEFI report if it is reported that the patient experienced an unspecified adverse reaction and there is no information on the type of adverse reaction.

ii. If the primary source has made an explicit statement that a causal relationship between the medicinal product and the reported adverse event has been excluded and the notified PRH agrees with this assessment, the report does not qualify as a valid ADR/AEFI report, since the minimum information for validation is incomplete (e.g. there is no suspected adverse reaction).

iii. An AEFI with only death as an outcome is a valid report and qualifies for reporting, however it must contain minimum criteria that is traceable to assist an investigation. Minimum criteria should include:

a) Patient identifiable criteria such as name and/or identification (IC) number and/or registration number;
b) Name of the facility where the death occurs;
c) Name of the facility which provide the vaccination;
d) Name of the primary reporter;
e) Suspected vaccine(s).

PRHs may be requested to assist the Authority by carrying out an investigation if required.

iv. Similar with suspected adverse reactions related to biological medicinal products (including biosimilar), the definite identification of the concerned products about their manufacturing is of importance. Therefore, all appropriate measures should be taken to clearly identify the names of the products and their batch numbers. With respect to this, it is recommended to specify in the case narrative if information on the batch number has been requested, when it is missing in the initially submitted ADR/AEFI report.

P3.2.2 Other Validation Criteria

P3.2.2.1 Non-Valid Report

i. The report is not valid if only an outcome (or consequence) is notified with no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance, a PRH is made aware that a patient was hospitalised or died, without any further information.

ii. In this situation, medical judgement should always be applied in deciding whether or not the notified information is an adverse reaction or an event.

iii. Lack of any of the four elements means that the case is considered incomplete and does not qualify for reporting as ADR/AEFI report. PRHs are expected to exercise due diligence in following-up the case to collect missing data elements and follow-up activities should be documented.

iv. A case which is not qualify for reporting, justification should be provided, and the case documented within the PV system for use in ongoing safety evaluation activities or when requested by the Authority.

P3.2.2.2 Missing Information

i. When the missing information has been obtained (e.g. when the medicinal product's causal relationship with the reported adverse event is no longer excluded), the ADR/AEFI report becomes valid for submission.

ii. A valid case of suspected adverse reaction initially notified by a consumer cannot be downgraded to a report of non-related adverse event if a contacted healthcare professional (who was nominated by the consumer for follow-up information) subsequently disagrees with the consumer's suspicion. In this situation, the opinions of both the consumer and the healthcare professional should be detailed in the narrative section of the ADR/AEFI report.

iii. Similarly, a solicited report of suspected adverse reaction should not be downgraded to a report of non-related adverse event, when the notified recipient (PRH) disagrees with the reasonable possibility of causal relationship expressed by the primary source on the supplied medicinal product. The opinions of both, the primary source and the recipient, should be recorded in the narrative section of the ADR/AEFI report.

iv. The same principle applies to the ADR/AEFI report seriousness criterion, which should not be downgraded from serious to non-serious if the notified recipient disagrees with the seriousness reported by the primary source.

P3.2.3 Follow-up of Reports

P3.2.3.1 Report that Require Follow-up

i. When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases.

ii. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, or cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum criteria for reports validation. Any attempt to obtain follow-up information should be documented.

P3.2.3.2 Follow-Up Methods

i. Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a safety concern.

ii. When information is received directly from a consumer suggesting that an adverse reaction may have occurred, and if the information is incomplete, attempts should be made to follow-up with the consumer to obtain consent to contact a nominated healthcare professional to obtain further information. When the case is subsequently confirmed totally or partially by a healthcare professional, the medical confirmation should be captured in the ADR/AEFI report.

iii. For some cases, it may not always be possible to perform follow-up activities, taking into account that the reporter information may have been anonymised in accordance with local legal requirements or due to provisions that allow for anonymous reporting, for example, in case of medication error with harm and the reporter does not wish to disclose an identity. These cases should be considered valid for submission as ADR/AEFI reports, providing that the notified organisation was able to confirm them directly with the primary sources and that the other minimum criteria for reports validation are satisfied.

iv. 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/AEFI reports should be clearly labelled as such.

v. 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.

vi. 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/AEFI cases should be as follows:

a) Serious and unexpected;
b) Serious and expected;
c) Non-serious and unexpected.

vii. 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. ADR/AEFIs under enhanced or active surveillance at the request of the Authority) as well as any cases that might lead to a labelling change.

P3.2.3.3 Follow-Up Significant Information

i. PRHs should submit follow-up ADR/AEFI reports if significant new medical information has been received. Significant new information relates to, for example, a new suspected adverse reaction, a change in the causality assessment, and any new or updated information on a case that impacts on its medical interpretation. Medical judgement should therefore be applied for the identification of significant new information requiring to be submitted as follow-up ADR/AEFI report.

ii. Situations where the seriousness criteria and/or the causality assessment are downgraded (e.g. the follow-up information leads to a change of the seriousness criteria from serious to non-serious, or the causality assessment is changed from related to non-related) should also be considered as significant changes and thus submitted as ADR/AEFI report.

P3.2.3.4 Follow-Up Non-Significant Information

i. In contrast, a follow-up report which contains non-significant information does not require to be submitted as ADR/AEFI report. This may refer, for example, to minor changes to some dates with no implication for the evaluation or submission of the case, or to some corrections of typographical errors in the previous case version.

ii. Medical judgement should be applied since a change to the birth date may constitute a significant modification (e.g. with implications on the age information of the patient). Similarly, a change of the status of a MedDRA code/term from current to non-current, due to a version change of MedDRA, can be considered as a non-significant change if this change has no impact on the medical content of a case.

P3.2.4 Data Management

P3.2.4.1 Record Maintenance

i. Confidentiality of patients’ records should always be maintained.

ii. Identifiable details of reporter should be kept in confidence, protected from unauthorised access. Strict control measures should be in place to provide access to documents and databases only to authorised personnel.

iii. Electronic data storage should allow traceability (e.g. audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

iv. A procedure should be in place to account for identification and management of duplicate cases.

P3.2.4.2 ADR/AEFI Description

i. The objective of the narrative is to summarise all relevant clinical and related information, such as patient characteristics, therapy dates, medical history, clinical course of the event(s), diagnosis, and ADR/AEFI(s), including the outcome, laboratory evidence (with normal ranges), and any other information that supports or refutes an ADR/AEFI (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 judgement to determine what information should be submitted.

P3.2.4.3 Standard Coding

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

P3.2.4.4 Cases from Two or More Sources

i. A mechanism should be in place to identify ADR/AEFI data that were reported to the PRH more than once or from a different source.

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

P3.2.4.5 Report Nullification

i. Multiple copies of the same ADR/AEFI reports should be nullified within the PV system and the record of nullification should be maintained, to allow auditing of the nullified record in the future.

ii. Documented procedures and processes should be in place to describe when ADR/AEFI reports may be nullified.

iii. Documentation related to nullified cases should be retained.

P3.2.5 Quality Management

P3.2.5.1 Quality Standard and Assurance of Case Report

i. PRH should have a Quality Management System (QMS) in place to ensure compliance with the necessary quality standards at every stage of case report documentation from collection, until case report archiving.

ii. Correct data entry, including the appropriate use of terminologies, should be quality controlled, either systematically or by regular random evaluation.

iii. Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof.

iv. About this, the source data (e.g. letters, emails, records of telephone calls, all of which includes details of an event) or an image of the source data should be easily accessible.

v. The whole process should be monitored by quality assurance audits.

vi. PRH should have documentation in place that clearly describe the roles, responsibilities and the required tasks of all parties involved. PRH should ensure that there is provision for proper control and, when needed, change of the system.

vii. This is equally applicable to activities that a third party has been engaged, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

P3.2.5.2 Quality Standard for Personnel Performing Pharmacovigilance Activities

i. Personnel directly performing pharmacovigilance activities should be appropriately trained in applicable pharmacovigilance legislation and guidelines, in addition to specific training in report processing activities for which they are responsible and/or undertake.

ii. Data entry personnel should be instructed in the use of the appropriate standards and terminologies, and their proficiency confirmed.

iii. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse events or adverse reactions collection and submission to the pharmacovigilance department in accordance with internal policies and procedures.

P3.3 ADR/AEFI REPORT BY SOURCE

When one party (the Authority or PRH) is made aware that the primary source may also have reported the suspected ADR/AEFI 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/AEFI report(s).

P3.3.1 Unsolicited Reports

P3.3.1.1 Spontaneous Reporting

i. A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a PRH that describes one or more suspected ADR/AEFIs 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/AEFI Reports

- Consumer ADR/AEFI 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.

P3.3.1.2 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 required.

iv. Clinical judgement should be used to determine the appropriate frequency of literature searches based on the active ingredient(s) of products registered under the PRH.

v. Only ADR/AEFIs which occurred in Malaysia, need to be reported to the Authority.

vi. Except for vaccine, 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 P3.2.1.2 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 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.

ix. If brand or trade name is not specified, the PRH should assume that it is its product and submit report to the Authority. The report should state that the specific brand is not identified.

P3.3.1.3 Information on Suspected ADR/AEFI from the Mass Media, Internet or Digital Media

i. The PRH-sponsored websites/programmes in mass media, internet or digital media should be screened regularly for potential reports of suspected ADR/AEFI.

ii. The non-PRH-sponsored website/programme should be included in the screening process once it has come to the knowledge of the PRH that the websites/programmes are related to the PRH's registered product.

iii. 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.

iv. The frequency of the screening should allow potential valid ADR/AEFI to be reported to the Authority within the stipulated timelines (see Appendix 2).

v. When collecting reports of suspected ADR/AEFIs 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 P3.2.1.1 and P3.2.1.2). Reports that are not qualified for reporting must be documented and kept for future reference.

vi. Unsolicited cases of suspected ADR/AEFI 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.

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

P3.3.1.4 ADR Reports Received Through the Authority

ADR reports received through the Authority (e.g. summary line-listing) should be considered as a source of unsolicited reports. However, the PRH are not required to resubmit these reports to the Authority as the purpose of this ADR report line-listing is to inform the PRH on the reports regarding their products received by the Authority in the specific timeline.

P3.3.2 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.

For the purposes of safety reporting, solicited reports should be classified as study reports, and therefore should have an appropriate causality assessment by a healthcare professional or the PRH. The causality assessment is important for the PRH to consider which suspected adverse reactions meet the criteria for reporting.

P3.3.2.1 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 subjected to protocol.

ii. The protocol should clearly describe the responsibility on the reporting of the ADR/AEFI suspected of being related to use of the medicinal product. The organisation supplying the medicinal product should continuously monitor the balance of benefit and risk of drugs used under such conditions.

P3.3.2.2 PRH Sponsored Studies

i. Studies subjected to post-market ADR/AEFI reporting requirements (e.g. phase IV studies) should be monitored in a way that ensures that all ADR/AEFI especially, serious expected and unexpected, 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. Except for AEFI, 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 roles in assessing the possible relationship between an adverse event and the administration of a product during post-marketing studies.

iv. It is the responsibility of the PRH/investigator to decide whether or not the active comparator drug reactions should be reported to the other PRH/manufacturer and/or directly to the Authority. The PRH/Investigator must report such events to either the PRH/manufacturer of the active control or to the Authority. Events associated with placebo will usually not fulfil the four (4) minimum criteria, therefore are not eligible for an expedited reporting.

P3.3.2.3 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 guideline 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 medicinal product(s).

P3.3.2.4 Post-Study Adverse Reactions

i. 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.

P3.4 REPORTING REQUIREMENTS IN SPECIAL SITUATIONS

P3.4.1 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 ADR/AEFIs 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/AEFI.

P3.4.1.1 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 questions 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:

   a) Reports of congenital anomalies or developmental delay in the foetus or the child;
   b) Reports of foetal death and spontaneous abortion;
   c) Reports of suspected ADR/AEFIs 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/AEFI. 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 (e.g. 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 no later than three (3) calendar days after first knowledge by PRH.

P3.4.1.2 Breastfeeding

Suspected ADR/AEFI(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 guideline.

P3.4.2 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.

P3.4.3 Lack of Efficacy

i. Reports of lack of efficacy should also be submitted to the Authority. Clinical judgement 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 (see 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 judgement 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 (see Appendix 2).

v. For vaccines, cases of lack of therapeutic efficacy should be reported, particularly in view to highlight potential signals of reduced immunogenicity in a sub-group of vaccines, waning immunity, or strain replacement. With regards 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.

P3.4.4 Reports of Overdose, Abuse, Off-Label Use, Misuse, Medication Error or Occupational Exposure

i. For the purpose of this guideline, 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 (either accidental or intentional), abuse, off-label use, misuse, medication error or occupational exposure, which has led to an ADR/AEFI, should be reported to the Authority.

iii. Reports with no associated ADR/AEFI 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 P8.1 Emerging Safety Issues).

iv. These reports 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, unregistered indication or population, etc.).

P3.5 ADR/AEFIs OCCURRING OUTSIDE MALAYSIA

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

PART 4:

Periodic Benefit-Risk Evaluation Report (PBRER)

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

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.

P4.1 INTRODUCTION

i. The PBRER described in this guideline 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 guideline, 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 (e.g. 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 underlie 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.

vi. PBRER need to include all collection of events which do not result in suspected ADR, even though not required to be reported as an individual case safety report (see Section P3.4.4).

vii. During pre-registration for new drug product/biologics, an existing PBRER is required to be submitted as part of the registration dossier [please refer to the current Drug Registration Guidance Document (DRGD)].

P4.2 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:

i. Summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;

ii. Summarising any important new efficacy or effectiveness information that has become available during the reporting interval;

iii. 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;

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

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 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 for entirely different indications. In these cases, the Authority should be notified and their agreement obtained, preferably at the time of approval.

For orphan medicines, the PRH shall provide an annual safety report in the event in which the requirement of PBRER cannot be fulfilled. The first annual safety report should be submitted no later than one month after the anniversary of the registration date in Malaysia.

The annual safety report should include:

i. A summary (line listing and summary tabulation) report of all the ADR cases received during a period of twelve months (see Appendix 4);

ii. A review of ongoing clinical study;

iii. Any risk minimisation activities or programmes requested by other authorities relevant to the registered orphan medicine;

iv. A description of the investigation plan for the coming year.

P4.3.2 Submission of PBRER for Products Other than New Drug Products/ Biologics

As a general rule, PBRERs for these medicinal products are not required. However, it may be requested when there is a safety concern affecting the benefit-risk balance of the registered product. It is expected that the PRH will monitor the safety of their products on the market and report any new safety information as soon as available.

The Authority may, for the purposes of assessing the safety and effectiveness of a drug, request the PRH to submit an Issue-Related Summary Report (IRSR). An IRSR contains a concise, critical analysis of the ADR and serious adverse drug reactions to a drug that are known to the PRH with respect to a specific issue that the Authority directs the PRH to analyse. A period of 30 calendar days or less is requested for the submission of the report, depending on the urgency of the issues. When the Authority requests the IRSR, it is preferred that it be submitted in the format defined in Appendix 5.

P4.3.3 Reference Information

An objective of a PBRER is to evaluate whether or not the 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 P4.4.2 (iii) 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 P4.4.2 (iii) 20 (Appendices)].

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 P4.4.2 (iii) 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 P4.4.2 (iii) 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, in addition to 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 guideline, 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 guideline 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. 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 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 six (6) months or longer.

An *ad hoc* PBRER may be requested by the Authority. *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.

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 authorities.

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 Submission Timeline for Post-Registration Requirement

As part of post-registration requirement for newly approved NDP [New Chemical Entity (NCE)] and Biologics products in Malaysia, PRH is required to routinely submit PBRERs, six (6) monthly for the first two (2) years after approval and annually for the subsequent three (3) years. The first PBRER submitted should have DLP no later than six (6) months after approval in Malaysia. For NDP (hybrid) products, the latest PBRER is expected to be submitted once in the following circumstances: new indication, new chemical form, new dosage form, new dosage strength and new route of administration.

In any cases the PBRER could not be submitted according to Malaysian PBRER submission requirement, the Authority should be notified, and their agreement obtained for a new schedule of PBRER submission.

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 six (6) or 12 months: within 70 calendar days;

ii. PBRERs covering intervals in excess of 12 months: within 90 calendar days;

iii. *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

For further guidance on the format and content of a PBRER, please refer to the ICH E2C (R2) Guideline on Periodic Benefit-Risk Evaluation Report (PBRER).

P4.5 ANNEX FOR PBRER SUBMISSION (FOR POST-REGISTRATION ONLY)

An annex is required for PBRER submission in post-registration phase. It should be submitted together with the PBRER for each submission. The annex should provide Malaysian specific information and includes the following sections:

i. Product overview in Malaysia

ii. Summary of safety changes:

a) Actions Taken in the Reporting Interval for Safety Reasons;
b) Changes in Reference Safety Information (RSI)
c) Action(s) Taken or Planned in Malaysia.

iii. List of signals evaluated

The appended **Annex for PBRER Submission** should be followed (see Appendix 3).

PART 5:

Risk Management Plan (RMP)

PART 5: RISK MANAGEMENT PLAN (RMP)

RMP is a document containing detailed description of the risk management system for a medicinal product.

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 during 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 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 (‘safety specification’).

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 (‘pharmacovigilance plan’).

c) Planning and implementation of risk minimisation, mitigation and assessment of the effectiveness of these activities (‘risk minimisation plan’).

vi. The risk management, is applicable to medicinal products at any point in their life cycle. However, this guideline is applicable to post-registration risk management. The risks addressed in this guideline 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 Definitions

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 RMP 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.

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.

The primary aim and focus of the RMP remains that of appropriate risk management planning throughout a medicinal product's life cycle. This includes the addition of safety concern where required, but also, as the safety profile is further characterised, the removal or reclassification of safety concerns.

i. Important potential risks can be removed from the safety specification in the RMP (e.g. when accumulating specific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important, or when there is no reasonable expectation that any pharmacovigilance activity can further characterise the risk), or they need to be reclassified to 'important identified risk' (e.g. if scientific and clinical data strengthen the association between the risk and the product).

ii. In certain circumstances, where the risk is fully characterised and appropriately managed, important identified risks may be removed from the safety specification (e.g. for products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimisation activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines).

iii. As the product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the area of missing information.

It is expected that over time the additional pharmacovigilance activities in the RMP will be completed and thus removed from the RMP. The need to continue additional risk minimisation activities may change, and some risk minimisation activities might need to be retained for the lifetime of the product.

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. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the applicant/PRH, whom should ensure oversight by someone with the appropriate scientific background within the company. Since a RMP is primarily a pharmacovigilance document, ideally the production of it should be managed by a qualified personnel (preferably the RPPV) with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure.

P5.4 OBJECTIVES OF A RISK MANAGEMENT PLAN

i. The main objectives of RMP are:

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

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

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

d) To document post-registration obligations that have been imposed as a condition for registration.

ii. As 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 wider target populations in everyday medical practice and so as to document the need for studies on efficacy in the post-registration phase (also known as effectiveness studies);

c) Include a description on 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 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 Submission of RMP for New Drug Products/Biologics

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

ii. During pre-registration for new drug product/biologics, RMP is required to be submitted as part of the registration dossier [please refer to the current Drug Registration Guidance Document (DRGD)].

iii. In the post-registration phase, an update is expected to be submitted in the following situations:

a) When there is a significant change to the benefit-risk balance of one or more medicinal products included in the RMP;

b) When there is an application involving a significant change to an existing registered product, such as:

- New or significant change in indication;
- New dosage form;
- New route of administration;
- New manufacturing process of a biotechnologically-derived product;
- New chemical form;
- New dosage strength.

c) When there is a change in the list of the safety concerns or any changes in the existing additional pharmacovigilance or additional risk minimisation activities;

d) At the request of the Authority when there is a concern on a risk affecting the benefit-risk balance.

P5.5.2 Submission of RMP for Products Other than New Drug Products/ Biologics

As a general rule, RMPs for these medicinal products are not required. However, a RMP may be requested when there is a safety concern affecting the benefit-risk balance of the registered product. It is expected that the PRH will monitor the safety of their products on the market and report any new safety information as soon as available.

P5.5.3 Submission Timeline for Post-Registration Requirement

An updated RMP should be submitted within 70 calendar days after the date of final sign off.

P5.6 STRUCTURE OF THE RISK MANAGEMENT PLAN

The RMP consists of seven (7) 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). RMP written in the European Union (EU) RMP format is acceptable.

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

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 (Including Post-Authorisation Safety Studies)

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 (RMP)

Part VII Malaysia-Specific Annex (MSA)

P5.6.1 RMP Part I: Product(s) 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:

i. Active substance(s);

ii. Pharmacotherapeutic group(s) (ATC code);

iii. Name of PRH or applicant;

iv. Date and country of first authorisation worldwide (if applicable);

v. Date and country of first launch worldwide (if applicable);

vi. Number of medicinal product(s) to which this RMP refers.

Administrative information on the RMP:

i. Data Lock Point of the current RMP;

ii. Date submitted and the version number;

iii. 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;

iv. RPPV details/signature on the finalised approved version of RMP.

For each medicinal product included in the RMP:

i. Invented name(s);

ii. Brief description of the product including:

a) Chemical class;

b) Summary of mode of action;

c) Important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);

iii. Indications;

iv. Dosage;

v. 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 e.g. both labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine the understanding of the benefit-risk profile during the post-registration 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:

i. Toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);

ii. General pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system);

iii. Drug interactions;

iv. 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 or 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:

i. Age and gender;

ii. Indication;

iii. Dose;

iv. 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, immune-compromised) 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 the use of tables or 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, e.g. populations that are considered under missing information.

Information on the low exposure of special populations or the lack thereof (e.g. pregnant women, breast-feeding women, patients with renal impairment, hepatic impairment or cardiac impairment, populations with relevant genetic polymorphisms, immune-compromised patients and populations of different ethnic origins) should be provided where available and as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the type of genetic polymorphism, as available.

If the product is expected to be used in populations not studied and there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be include as missing information in the RMP.

Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, e.g. “on-label”, and if the use in such populations might be associated with the risks of clinical significance.

If there is evidence that use in excluded populations is associated with an undesirable clinical outcome, then the outcome should be included as an important (potential) risk.

P5.6.2.5 Module SV: Post-Authorisation Experience

This module should include discussion on post-marketing data that are available from post-authorisation experience in other regions where the product is already registered or post-marketing data from other registered products containing the same active substance from the same PRH. It should only provide an overview of experience in the post-authorisation phase to help in risk management planning purposes.

Additionally, a discussion on how the product is being used in practice and on-label and off-label use, including its use in the special populations mentioned in RMP module SIV, may also be included when relevant for the risk identification discussion in module SVI.

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. It may also include other safety topics that may lead to risks of the product such as potential harm from overdose, potential risks resulting from medication errors and off-label use, potential for transmission of infectious agents from the manufacturing process, the important pharmacological class effects, the important pharmacokinetics and pharmacodynamics interactions and the risks associated with the administration procedure and disposal of the used product.

SVI.1 Identification of Safety Concerns in the Initial RMP Submission

Initial identification of safety concerns (important identified and important potential risks during the initial application for registration or post-registration (e.g. for approved products that previously did not have an RMP). This section is expected to be “locked” and not change after approval of the initial RMP.

SVI.2 Risks Considered Important for Inclusion in the List of Safety Concerns and Risks Not Considered Important for Inclusion in the List of Safety Concerns

The following information should be summarised and discussed in this section: risk seriousness, risk frequency and the benefit-risk impact of the risks.

For risks not taken forward as safety concerns, the information can be grouped by reasons for not including them as safety concerns.

SVI.3 New Safety Concerns and Reclassification with A Submission of An Updated RMP

When an important identified or potential risk or missing information is re-classified or removed, a justification should be provided in this section, with appropriate reference to the safety data.

SVI.4 Details of Important Identified and Potential Risks and Missing Information

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 CCDS.

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 likely to be included in the Contraindications or Warnings and Precautions section of the package insert or the CCDS should be included here.

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

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:

i. Frequency;

ii. Public health impact (severity and seriousness/reversibility/ outcomes);

iii. Impact on the individual patient (effect on quality of life);

iv. Risk factors (including patient factors, dose, at risk period, additive or synergistic factors);

v. Preventability (e.g. predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);

vi. Potential mechanism;

vii. Evidence source(s) and strength of the evidence.

The frequency of important identified risks should be expressed by taking into account the source of the data. For a product already on the market, the reporting rate which is 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 therefore 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-prescription 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.

Presentation of missing information data:

i. Name of the missing information (using MedDRA terms when appropriate);

ii. Evidence that the safety profile is expected to be different than in the general target population;

iii. Description of a population in need of further characterisation or description of the risk anticipated in the population not studied, as appropriate.

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:

i. Important identified risk; or

ii. Important potential risk; or

iii. Missing information.

P5.6.3 RMP Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies/PASS)

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:

i. The identification of new safety concerns;

ii. Further characterisation of known safety concerns including severity, frequency and risk factors;

iii. The investigation of whether a potential risk is confirmed as an identified risk or refuted;

iv. How important missing information will be sought.

The pharmacovigilance plan should be based on the safety concerns summarised in RMP module SVII 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.

This RMP section should describe only the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection. The PRH should list in this RMP section their planned additional pharmacovigilance activities, detailing what information is expected to be collected that can lead to a more informed consideration of the benefit-risk balance.

Additional pharmacovigilance activities are pharmacovigilance activities that are not considered routine. The post-authorisation safety studies (PASS) may include non-clinical studies, clinical trials or non-interventional studies. Examples include long-term follow-up of patients from the clinical trial population or a cohort study to provide additional characterisation of the long-term safety of the product.

PASS aim to identify and characterise risks to collect further data where there are areas of missing information or to evaluate the effectiveness of additional risk minimisation activities. They should relate to the safety concerns identified in the safety specification, be feasible and should not include any element of a promotional nature.

PASS should be designed and conducted according to the respective legislation in place. Study protocols may be included for evaluation in an RMP update only when the studies are included in the pharmacovigilance plan and the protocols submission has been requested by the competent Authority. Protocols of completed studies should be removed from RMP once the final study reports are submitted to the competent Authority for assessment and the study is removed from the pharmacovigilance plan. The milestone for the final study report submission to the competent Authority should be included for all studies in the pharmacovigilance plan.

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

This part of the RMP should include a list of post-authorisation efficacy studies (PAES) imposed as conditions to the marketing authorisation or when included as specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances. If no studies are required, it should be stated as such.

P5.6.5 RMP Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

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.

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, e.g. products where the indications lie in different medical specialties and have different safety concerns associated; products where risks differ according to target population; products with legal status for the supply of medicinal products to patients.

The need for continuing risk minimisation measures should be reviewed at regular intervals and the effectiveness of risk minimisation activities assessed.

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. DHPC/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective.

P5.6.5.1 Routine Risk Minimisation Activities

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

i. Package insert;

ii. Product label(s);

iii. Consumer Medication Information Leaflet (RiMUP);

iv. Pack size(s);

v. Legal status of the product.

P5.6.5.2 Additional Risk Minimisation Activities

Additional risk minimisation activities, if proposed, need to be provided in detail with a justification for the proposed activity. The need to continue such measures should be periodically reviewed by the PRH. Any subsequent changes/updates should be notified and approved by NPRA prior to implementation.

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 the Risk Management Plan

The summary must include key elements of the RMP with a specific focus on risk minimisation activities. With regards to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information.

The RMP summary should be updated when important changes are introduced into the full RMP. Changes should be considered important if they relate to the following:

i. New important identified or potential risks or important changes to or removal of a safety concern;

ii. Inclusion or removal of additional risk minimisation measures or routine risk minimisation activities recommending specific clinical measures to address the risk;

iii. Major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies).

P5.6.7 RMP Part VII: Malaysia-Specific Annex (MSA)

A Malaysia-Specific Annex (MSA) is required for RMP submission. It should be submitted together with the RMP for each submission. The MSA should provide Malaysian specific information and includes the following sections:

i. Product overview in Malaysia

ii. Changes from previous RMP version

iii. Summary of changes to the MSA over time

iv. Safety specification: summary of safety concerns in relation to the approved indication(s) in Malaysia.

v. Description of local pharmacovigilance plan

vi. Description of local risk minimisation plan

vii. Additional Information (if applicable):

a) Latest version of the proposed/approved Malaysian package insert.

b) Latest version of the proposed/approved Consumer Medication Information Leaflet (RiMUP).

c) Details of local additional pharmacovigilance activities, e.g.:

- Tabulated summary of planned, ongoing and completed pharmacovigilance study programme;
- Protocols for proposed, ongoing, and completed studies in pharmacovigilance plan;
- Specific adverse event follow-up forms;
- Protocols for proposed and ongoing studies in RMP Part IV.

d) Details of local risk minimisation activities, e.g.:

- Approved Direct Healthcare Professional Communication (DHPC) Letter;
- Educational materials provided to healthcare professionals (English version) and patients (both English and Malay versions).

e) Other supporting data (including referenced materials)

- Any additional risk minimisation activities/programmes requested by other regulatory authorities including EU should be provided.

The appended **Template for Malaysia-Specific Annex (MSA)** should be followed (see Appendix 6).

PART 6:

Pharmacovigilance System Master File (PSMF)

PART 6: PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)

While a pharmacovigilance system is a system used by PRH to fulfil its pharmacovigilance tasks and responsibilities designed to monitor registered products' safety and any changes to their benefit-risk balance, the Pharmacovigilance System Master File (PSMF) is **a detailed description** of the system used. This part provides detailed guidance regarding the requirements for the PSMF in Malaysia, including its maintenance, content and associated submissions to the Authority.

Since PSMF provides detailed description of the pharmacovigilance system within a PRH, it reflects the PRH's readiness and competency in pharmacovigilance. The PSMF could also provide general insights on the pharmacovigilance system of the PRH to the Authority. A PRH may be required to submit PSMF to the Authority in circumstances whereby an assessment of its pharmacovigilance system is warranted such as prior to a Good Pharmacovigilance Practice Inspection (GVPI) and as per requirement of the Conditional Registration of Pharmaceutical Products during Disaster. More details on the Malaysian GVPI will be announced in the future.

On the other hand, the Pharmacovigilance System Summary (PVSS) is a document that briefly describes or summarises the pharmacovigilance system of the **PRH in Malaysia**. The PVSS serves as a commitment document by the PRH to develop a PSMF and to establish a PV system within the company. The PVSS is also part of the requirements to be fulfilled by PRH as laid out in the Guidance and Requirements on Conditional Registration of Pharmaceutical Products during Disaster. Apart from this, PVSS may be used by the Authority for risk-based assessment to prioritize PRHs for inspection in GVPI.

P6.1 STRUCTURES AND PROCESSES

i. The PSMF is applicable for any human medicinal product registered in Malaysia, irrespective of the product registration procedure or marketing status (except for cosmetic product and veterinary product).

ii. The content of the PSMF should mainly contain details of Malaysian pharmacovigilance activities and local availability of safety information for medicinal products registered in Malaysia. Regional and /or global information or activities should only be included when necessary to reflect the overall pharmacovigilance system of the PRH.

P6.1.1 Objectives

The objective of PRH having the PSMF is to ensure a pharmacovigilance system has been implemented in accordance with the Malaysian requirements.

P6.1.2 Submission and Maintenance of PV System Summary (PVSS) and PSMF

a) All PRHs are required to prepare both PVSS and PSMF. However, submissions of PVSS and PSMF to the Authority are applicable only to PRHs involved in GVPI and the timeline of submission will be notified by the NPRA. Under this scenario, maintenance and submission of the updated PSMF is applicable. For submission of PVSS and PSMF under conditional registration, please refer to the related guidelines such as the Guidance and Requirements on Conditional Registration of Pharmaceutical Products during Disaster.

   Details of Malaysian GVPI will be announced in the future.

   All PRHs that are involved in GVPI are required to submit two (2) documents to the Pharmacovigilance Section, Centre for Compliance and Quality Control, NPRA:

   - Pharmacovigilance System Summary (PVSS)
   - Pharmacovigilance System Master File (PSMF)

b) The Pharmacovigilance System Summary, PVSS (see Appendix 7 for the sample) should contain:

   - A statement signed by the PRH to ensure that the PRH has established a pharmacovigilance system in accordance with the requirements;
   - A commitment to develop a PSMF;
   - Organisational structure of the PRH relevant to the pharmacovigilance system, including the operating system of the pharmacovigilance unit;
   - A brief description on the pharmacovigilance system/database;
   - A list of all registered products (except TMHS products);
   - A list of products registered under New Drug Product (NDP) category;
   - A list of products registered under Biologic category;
   - A list of products registered under Prescription category;
   - A list of products registered under Non-Prescription category;
   - A list of products with special condition for registration;
   - A list of products listed under current Ministry of Health (MOH) tender;
   - A list of products listed under current National Immunisation Programme (NIP);
   - A list of products categorised as Orphan Medicine;
   - Number of ADR/ AEFI reports submitted to NPRA over the past 12 months*;
   - The contact details and curriculum vitae (CV) of the RPPV and local contact person (if applicable), and back-ups for both.

   * Note: 12 months' timeline shall be determined by PRH as appropriate

c) The PVSS sample is available at Appendix 7. PVSS is expected to be submitted **only once** for each PRH, **unless requested by the Authority**. No maintenance of PVSS is expected from the PRH. Submission of PVSS should be in hardcopy.

d) Until further announcement, PVSS and PSMF for **traditional medicines and health supplement (TMHS) products are not required to be prepared and submitted**. However, it is expected that PRH will continue to maintain and monitor the pharmacovigilance activities for TMHS products.

e) As the PSMF content will continue to be updated from time to time, all changes should be recorded in the logbook in Annex I. However, any changes in these situations require a notification to be submitted to the NPRA:

- changes in RPPV, local contact person and the back-up personnel contact details;
- changes in PV safety database (e.g. data migration);
- changes in significant service provider, especially concerning the reporting of safety data;
- organisational changes, such as takeovers, mergers impacting structure and responsibilities of PV function.

Note:

- There is no specific format for the notification to the NPRA.
- Timeline to notify NPRA (through email) is within 30 calendar days from the effective date of changes or after first knowledge by PRH. For changes in RPPV, local contact person and the back-up personnel contact details, timeline to notify (through email) NPRA is within 30 calendar days from the effective date of the changes (refer P6.1.3). Only those involved in GVPI need to notify PSMF updates to the NPRA (Pharmacovigilance Section, NPRA). For changes in RPPV, local contact person and the back-up personnel contact details, please refer to P6.1.3(c).
- For these changes, updated PSMF (CD/ USB flash drive) will only be required to be submitted if requested by NPRA. Timeline to submit updated PSMF will be on case to case basis and will be communicated by NPRA.

P6.1.3 Person Responsible for PSMF

a) As part of the pharmacovigilance system, the PRH must have permanently and continuously at its disposal an appropriately responsible person for PV (RPPV) activities (See Section P2.1.2), including developing and updating the PSMF.

b) The RPPV should preferably be based in Malaysia, However, in the event where the RPPV is based outside Malaysia (e.g. Singapore), the Authority would require a contact person to be based in Malaysia. The local contact person must be contactable by the Authority at all times and he or she may then consult the RPPV for any issues pertaining to PV. The details of both the local contact person and the RPPV must be informed to the Authority.

c) All PRHs are required to continuously inform the Authority on any changes to the contact details of the RPPV, local contact person (if applicable) and all back-up personnel. The acceptable timeline to inform the Authority is within 30 calendar days from the effective date of the changes. This requirement applies to all PRH regardless of their participation in GVPI. In addition, PRHs that participate in the GVPI, should also update the current PSMF on any changes to these contact details.

d) During a GVPI, the RPPV and local contact person (if applicable) are expected to attend the inspection.

P6.2 THE REPRESENTATION OF PHARMACOVIGILANCE SYSTEM

i. The PSMF shall describe the pharmacovigilance system for one or more medicinal products of the PRH. For different categories of medicinal products (e.g. vaccines, health supplements, etc.), the PRH may apply a different or the same pharmacovigilance system.

a) If the PRH wishes to have different pharmacovigilance systems, each system shall be described in a separate PSMF [one (1) pharmacovigilance system described in one (1) PSMF]. Those files shall cumulatively cover all medicinal products of the PRH.

b) Alternatively, if the PRH wishes to apply the same pharmacovigilance system for all categories of products, only one (1) PSMF is required.

ii. For subsidiary companies, the PRH may:

a) Apply separate pharmacovigilance systems and subsequently separate PSMF for each company even though the same pharmacovigilance system covers products from more than one PRH, e.g. one (1) pharmacovigilance system described in two (2) PSMF for two (2) subsidiary companies;

b) Alternatively, if a pharmacovigilance system is shared, each PRH is responsible in ensuring that a PSMF exists to describe the pharmacovigilance system applicable for its products. In short, several PRHs (of subsidiary companies only) are allowed to share the same pharmacovigilance system and PSMF, e.g. one (1) pharmacovigilance system described in one (1) PSMF for two (2) subsidiary companies.

iii. The PRH may also engage a third party to carry out responsibility as RPPV and local contact person (if applicable) or some activities in the pharmacovigilance system or the development of a PSMF. However, the PRH retains ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF, maintenance of the PSMF and its provision to the Authority upon request. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

iv. In the scenario of shared pharmacovigilance system by several PRHs (only applicable for subsidiary companies), activities for maintaining the PSMF in a current and accessible state should be properly delegated and the person responsible for the PSMF should be properly assigned. Ideally, one (1) PSMF shall only be assigned to one (1) RPPV and local contact person (if applicable). However, a single RPPV and local contact person (if applicable) may be assigned to more than one PSMF, depending on his or her capability.

v. Where applicable, a list of all PSMFs held by the same PRH shall be provided in the Annexes (see Section P6.3.8.); this includes the details of the RPPV and local contact person (if applicable) and the relevant product(s).

vi. Updates to the PSMF must be done on a timely manner as the pharmacovigilance system may change with time. Since a specific RPPV and local contact person (if applicable) is responsible for the pharmacovigilance system, changes to the PSMF should be notified to him or her in order to support his or her authority to make improvements to the system. The PRH should promptly inform the Authority on any changes or update made to the PSMF (see Section P6.1.2) as well.

vii. The RPPV and local contact person (if applicable) should be in a position to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under his or her responsibility to the Authority.

P6.3 CONTENT OF THE PSMF

The content of the PSMF should be indexed following the modular system described in the sections below and the annex headings described in section P6.3.8. The structure of PSMF should be according to the below listed primary topic sections and contain fundamental information to describe the pharmacovigilance system. Detailed information that may change frequently could be referred to and contained in the Annexes. See Section P6.4 for change control associated with the change of content in PSMF.

P6.3.1 Responsible Person for PV (RPPV), RPPV back-up, local contact person (if applicable) and local contact person back-up (if applicable)

i. The information relating to the RPPV, RPPV back-up, local contact person (if applicable) and local contact person back-up (if applicable) shall include:

   a) A summary curriculum vitae with the key information on the role of the RPPV, local contact person (if applicable) and their respective back-up;

   b) Contact details (including position in company, address, telephone number, fax number, emergency contact number and email address);

   c) Details of back-up arrangements to apply in the absence of the RPPV and local contact person (if applicable).

ii. If the RPPV, local contact person (if applicable) and their respective back-up is provided by a third party (contract), the name of the company the person works for should also be provided.

iii. A list of tasks that have been delegated by the RPPV shall be included in the Annex. The list should outline the activities that are delegated, to whom and the accessibility to a medically qualified person if applicable.

P6.3.2 Organisational Structure of the PRH

i. The content of the PSMF should mainly contain details of Malaysian pharmacovigilance activities (see Section P6.1).

ii. This section should provide a description of the organisational structure of the PRH relevant to the pharmacovigilance system. A clear overview of the company(s) involved (including third parties), the main pharmacovigilance departments and the relationship(s) between organisations and operational units relevant to the fulfillment of pharmacovigilance obligations is expected.

iii. The organisational structure should be showing the position of the RPPV and local contact person (if applicable) in the organisation. Diagrams may be particularly useful with the name of the department or third party clearly indicated.

iv. The organisational structure should be able to reflect the site(s) where the pharmacovigilance functions are undertaken, including but not limited to individual case safety report collection, evaluation, safety database case entry, PSUR/PBRER production, RMP management, signal detection and analysis, data evaluation and decision-making with regards to safety issues as well as management of safety variations to products whichever related.

v. The description of organisational structure should clearly list down system/database/vendors (third parties) that are involve in Malaysian Pharmacovigilance system/activities and system/database/vendors (third parties) that contribute to and/or interfere with the Malaysian Pharmacovigilance system/activities. This may be in the form of a list or table to show the parties involved, the roles undertaken and the concerned product(s).

vi. The delegated pharmacovigilance activities should also be described in this section, including arrangements with other parties to reflect the company's overall/whole picture of the pharmacovigilance system in Malaysia.

vii. Links with other organisations, such as co-marketing agreements and engagement of a third party on pharmacovigilance activities should be outlined. A description or a summary of the contracts and agreements relating to the fulfillment of pharmacovigilance obligations should be provided. This may be shown in a list or table on the parties involved, the roles undertaken and the concerned product(s). The list or table can be organised according to:

a) Service providers (e.g. medical information, auditors, patient support programme providers and etc.);

b) Commercial arrangements (distributors, licensing partners, co-marketing and etc.);

c) Other technical providers (hosting of computer system and etc.)

The list should be provided in the Annexes (see Section P6.3.8).

viii. All records (including, but not limited to, contractual agreements, letter of appointment, official document and safety data or ADR data) should be available on the premises of the PRH for auditing and inspection purposes.

P6.3.3 Sources of Safety Data

i. This section should describe the safety data collection process, including all parties responsible, for solicited and spontaneous case collection for products registered in Malaysia. This should include medical information sites (e.g. company sponsored or owned websites/any mass media) as well as affiliate offices and contractual parties.

ii. The information may be provided in a list, describing nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and email) for the site. The list may be located in the Annexes. The description or summary of the agreements, letter of appointment and official document should be made available in section P6.3.2 and P6.3.8.

iii. The focus should be on activities in Malaysia. However, global information or global activities may be elaborated if deemed necessary. A flow diagram may be used to show a clear picture of the process for ICSRs from collection to reporting to the Authority with indication of the departments and/or third parties involved.

iv. The ADR report line-listing from the Authority (source of safety data) should be reviewed and recorded.

P6.3.4 Computerised Systems and Databases

i. This section should describe the location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose. The computerised system that should be described includes all computerised system and database that are used in performing all PV activities and especially those related to the source of safety data.

ii. If the computerised system is not applicable, a paper-based system may be used. The paper-based system must be able to reflect a systematic approach of managing the safety information.

iii. Where multiple computerised systems and/or databases are used, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerisation within the pharmacovigilance system can be understood.

iv. The management of data, mechanisms used to assure the integrity, change control, validation status of key aspects of system functionality, back-up procedure and accessibility of the safety data to collate information about ADR should be described.

P6.3.5 Pharmacovigilance Processes

i. This section describes the overview of pharmacovigilance process (e.g. standard operating procedures, manuals in Malaysia and/or global level), data handling (e.g. the type of ICSR retained) and records (e.g. safety database and paper file) for the performance of a pharmacovigilance system.

ii. The description must be accompanied by the list of processes, as well as interfaces with other functions. Interfaces with other functions include, but are not limited to, the roles and responsibilities of the RPPV and local contact person (if applicable), responding to the Authority requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annex, should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

iii. The details required shall be including, but not limited to:

a) ADR case collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities (if applicable);

b) PBRER scheduling, production and submission (if applicable);

c) Communication of safety concerns to consumers, healthcare professionals and the Authority;

d) Implementation of safety updates to the label, package insert (PI) and consumer medication information leaflet (RiMUP);

e) Risk management system and monitoring of the outcome of risk minimisation measures (if applicable);

f) Monitoring of product risk-benefit profile(s), the result of evaluation and the decision making process; this should include signal generation, detection and evaluation (if applicable).

P6.3.6 Pharmacovigilance System Performance

i. This section should show the **target** and **evidence** of the pharmacovigilance system performance. Hence, this section should include a description of the monitoring methods applied and contain (the following as a minimum):

a) An explanation on assessment of correct reporting of ICSR. Figures and/or graphs should be able to show the timeliness reporting over the past years in the Annex;

b) An overview of the timeliness of PBRER reporting to the Authority (if applicable). The Annex should be able to reflect the latest figures as a proof of compliance assessment;

c) An overview of the methods used to ensure timeliness of safety variation submissions to the Authority, including the tracking of required safety variations that have been identified but not yet been submitted;

d) An overview of adherence to RMP commitments or other conditions of product registration(s) relevant to pharmacovigilance (if applicable).

ii. A list of **performance indicators** must be provided in the Annex to the PSMF, together with the **results of performance measurements**.

P6.3.7 Quality System

i. This section describes the quality management to the organisational structure and pharmacovigilance system. This shall include:

a) **Document and record archive**. Provide a description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF, as well as other pharmacovigilance records and documents;

b) **Procedural documents**. The control, accessibility, implementation and maintenance of documents (e.g. standards, operating procedures, work instructions and etc.) used in pharmacovigilance should be described. The applicability of the various documents at global, regional or local level within the organisation or under control of third parties should be clearly stated;

c) **Training**. All personnel involved in the pharmacovigilance activities shall receive initial and continued training. This training shall relate to the roles and responsibilities of the personnel.

Adequate training should also be considered by the organisation for staff members with no specific pharmacovigilance tasks and responsibilities assigned to them but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance (e.g. telephone operators, receptionists, etc.). Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, sales and marketing, regulatory affairs and legal affairs.

The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel. The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities.

There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

Appropriate instructions on the processes to be used in case of urgency, including business continuity shall be provided by the organisation to their personnel.

A summary description of the training concept and planning should be included. The evidence of training (training record), training plan and the training material used may be added in the Annex of PSMF.

d) **Auditing**. Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system.

The PSMF should contain a note associated with any audit where significant findings are raised. This means that major or critical findings must be indicated. The audit report must be documented into the quality system.

In the PSMF, it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s).

Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.

The audit strategy should cover all parts of the pharmacovigilance system including:

a) All pharmacovigilance processes and tasks;

b) The quality system for pharmacovigilance activities;

c) Interactions and interfaces with other departments, as appropriate;

d) Pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. PRH affiliates or third parties, such as contract organisations and other vendors).

A description of the approach used to plan audit, scheduled and completed audits, including the date(s) (of conduct and of report), scope, results, completion status, significant findings, corrective and/or preventative action(s) and anticipated solution date(s) should be clearly stated in the Annex of PSMF.

P6.3.8 Annexes

i. The fundamental information of the pharmacovigilance system has been described under section P6.3.1 – P6.3.7. All the detailed information that may change frequently should be stated in the Annexes. This section describes the minimum Annexes that are required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however the Annexes should be named accordingly. For example, Annex E should not be renamed to Annex D in circumstances where no Annex concerning computerised systems and databases is used. Annex D should simply be described as “not available” in the indexing.

ii. Where pharmacovigilance systems are shared (only applicable for subsidiary companies), all products that utilise the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The product list may be presented separately for each PRH. Alternatively, a single list may be used, which is supplemented with the name of the PRH(s) for each product.

iii. **Annex A, Responsible Person for PV (RPPV), RPPV back-up, Local contact person (if applicable) and local contact person back-up (if applicable)**. The details should include but not limited to:

a) Roles and responsibilities of the RPPV and local contact person (if applicable) and the delegation of activities;

b) Curriculum vitae;

c) Contact details.

iv. **Annex B, Organisational structure of the PRH.** The details should include but not limited to:

a) List of contractual agreements/letter of appointment/official document;

b) Organisation chart;

c) Flow chart of pharmacovigilance activities and related departments.

v. **Annex C, Sources of safety data**. The details should include but not limited to:

a) Lists of sources of safety data;

b) Brief description of the sources;

c) Flow chart for processing of ADR reports;

d) List of studies, registries, surveillance or support programmes (if applicable).

vi. **Annex D, Computerised systems and databases**. The details should include but not limited to:

a) List of service provider and vendor for computerised system of the company (if applicable).

vii. **Annex E, Pharmacovigilance processes**. The details should include but not limited to:

a) List of procedural documents (list all procedural documents contributing directly and/or indirectly to local pharmacovigilance activities).

viii. **Annex F, Pharmacovigilance system performance**. The details should include but not limited to:

a) List of performance target and indicators;

b) Current results of performance assessment in relation to the indicators.

ix. **Annex G, Quality system**. The details should include but not limited to:

a) List of audit schedules;

b) List of audits conducted and completed;

c) List of training attended by PV staff;

d) Training material used (e.g. presentation slides, posters, handouts, quiz form).

x. **Annex H, List of medicinal products (except TMHS products) covered by the pharmacovigilance system**. The details should include but not limited to:

a) The list of medicinal products covered by the pharmacovigilance system registered in Malaysia (regardless of current status) should be presented in a table with the below information:

- Active ingredient;
- Product name (same as the registered name);
- Product registration number (MAL number);
- Product registered category (e.g. biologics, new drug product, prescription and non-prescription);
- Product registration status (e.g. approved, special condition of registration);
- Marketing status.

b) Where applicable, a list of other PSMF held by the same PRH should be included. The list should include the PSMF reference number, name of PRH, name of RPPV and local contact person (if applicable) for the pharmacovigilance system used. The name of the service provider should be included if the system is managed by a third party company.

Note: The PSMF reference number given is for **identification purpose only**. The reference number will be given during the submission of PV system summary.

xi. **Annex I, Log book & History of changes for Annex contents** (see Section P6.4). The details should include but not limited to:

a) Log book;

b) History of changes for annex contents.

P6.4 LOGBOOK AND HISTORY OF CHANGES FOR ANNEX CONTENTS

i. All changes to the PSMF should be recorded. The changes to the content of the master file must be descriptive (include date and nature of change) and recorded in the logbook that is available in Annex I. The record for history of changes encompasses the pharmacovigilance safety database, significant pharmacovigilance service provider, merger and delegation of PSMF management.

ii. The RPPV should always be kept informed of such changes as well.

iii. The **history of changes** in each related Annex (e.g. product list, standard operating procedure list and compliance figures) should also be regularly updated.

iv. The superseded versions of such content may be managed outside of the PSMF content itself and made available to the Authority if requested. The PSMF should provide a description of the pharmacovigilance system at the current time, though the function and scope of the pharmacovigilance system in the past may need to be understood.

v. PRHs should have document control procedures in place to govern the maintenance of the PSMF, including those who have engaged a third party on the PSMF service. The RPPV and relevant third parties should be kept informed in order to ensure that this change control is fully implemented.

P6.5 PSMF PRESENTATION

i. The Malaysian PSMF can be written in English or Malay language, indexed in a manner consistent with the headings described.

ii. The Malaysian PSMF may be in an electronic or a hard copy form. The electronic form of PSMF should be made available as hard copy upon request from the Authority. The PSMF must be available (electronic or hard copy form) during a GVPI.

iii. The PSMF should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes.

iv. The cover page of PSMF should include:

a) The name of the PRH;

b) The name of any other concerned PRH (sharing the same pharmacovigilance system, only applicable for subsidiary companies);

c) The name of RPPV and local contact person (if applicable) (the person responsible for the particular PSMF);

d) The third party company name of the relevant RPPV and local contact person (if applicable) (if a third party is engaged);

e) The list of PSMF for the PRH (if more than one pharmacovigilance system);

f) The date of prepared/last update and version number;

g) The Malaysian PSMF reference number (will be provided upon submitting the PV system summary).

PART 7:

Miscellaneous

PART 7: MISCELLANEOUS

P7.1 EMERGING SAFETY ISSUES

Safety issues considered by a PRH to require urgent attention by the Authority because of the potential major impact on the safety or risk-benefit balance of the product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals. Examples include but are not limited to:

i. Safety-related actions by regulatory agencies in reference countries and European Medicines Agency (EMA) such as:

   a) The withdrawal or suspension of the medicine's availability (except for solely business decisions);

   b) The addition or modification of a contraindication, warning or precaution statement to the product information or label for safety reasons;

   c) The modification or removal, of an indication for safety reasons.

ii. Changes in the nature, severity or frequency of known serious adverse reactions.

iii. Detection of new risk factors for the development of a known adverse reaction or a new adverse reaction that may impact on the safety or benefit-risk balance of the medicine.

iv. An unusual and significant lack of efficacy occurring in or outside Malaysia that may have implications for public health.

v. Major safety findings from a completed non-clinical study, post-registration study or clinical trial that may impact the safety or risk-benefit balance of the medicine.

vi. A signal of a possible teratogenic effect or of significant hazard to public health.

The examples above are not intended to be an exhaustive list of emerging safety issues, and it is up to PRH to assess safety issues on a case-by-case basis and evaluate whether this has an impact on the medicine's safety or risk-benefit balance and/or implications for public health.

All pertinent factors should be taken into account when assessing a safety issue. Issues to consider include the medicine, the risks involved and the regulatory context. If the PRH determines after appropriate assessment that a safety issue is not an emerging safety issue and do not report it, the PRH should document a justification for this decision. This documentation may be requested by the Authority at any time. If in doubt about a safety issue, treat it as an emerging safety issue.

A safety issue leading to regulatory action in reference countries and EMA should be reported to the Authority regardless of whether the PRH agrees with their recommendations and conclusions.

These safety issues, which may affect the safety or 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. Generally, emerging safety issues should be notified to the Authority no later than three (3) calendar days upon knowledge of the PRH. However for issues which involve withdrawal/suspension of registration due to emerging safety issues outside the country, they should be notified within 24 hours after first knowledge by the PRH (see Appendix 2). Only actions that have taken place need to be notified to the Authority, not actions that are being contemplated.

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 registered product.

P7.2 SAFETY EVALUATION BY THE PHARMACOVIGILANCE SECTION, NPRA

As part of safety evaluation process, Pharmacovigilance Section, NPRA may request additional safety documents from the PRH to assist the evaluation. Should the safety issues warrant any regulatory action (e.g. product information update), PRH will be notified and the proposed documents from the PRH will be assessed accordingly for finalization before PRH submit the documents through variation process in the Quest online system. However, if not notified, PRH must always be vigilant of any directives issued out by the DCA on any product information update and take further action as required.

P7.3 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.

P7.3.1 Direct Healthcare Professional Communication (DHPC)

A Direct Healthcare Professional Communication (DHPC) is 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 intended to be used as:

i. Replies to enquiries from healthcare professionals;

ii. Communication tools to inform healthcare professionals on any misinformation in the PI/RiMUP due to errors made by the PRH;

iii. As educational materials for routine risk minimisation activities;

iv. A platform to announce new product launch.

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 DHPC 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 **Template for Direct Healthcare Professional Communication** should comply to format (see Appendix 8).

Further recommendations on DHPC:

i. Safety information should be clear and concise; it should not exceed three (3) pages;

ii. The reason for dissemination should be explained (e.g. availability of new data);

iii. Recommendations to healthcare professionals should be given on how to minimise risk, if known and information for the general public;

iv. 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.

Once the DHPC has been finalised, the PRH should submit to the Authority the final signed DHPC before it could be distributed to the recipients accordingly. A notification to the Authority should be submitted upon completion of distribution (within the proposed timeline) to complete the process of DHPC communication.

P7.3.2 Consumer Medication Information Leaflet (RiMUP)

Please refer to the latest version of *Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna* for further details.

P7.4 OTHERS

P7.4.1 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 boxed warning 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.

ASSOCIATED DOCUMENTS

APPENDIX 1: ADR/AEFI REPORTING FORMS

REPORT ON SUSPECTED ADVERSE DRUG REACTIONS

NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING

Email: fv@npra.gov.my Website: www.npra.gov.my

(Please report **all** suspected adverse drug reactions including those for vaccines, health supplements 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. Identities of Reporter, Patient and Institution will remain **Confidential**.)

REPORT No. (*for official use only*): .....

PATIENT INFORMATION

I.C. No. / R/N / Initials | *Age | *Gender *(please tick)* Male ☐ Female ☐ | Wt (kg) | *Ethnic Group | *Please tick (if applicable):* ☐ Initial Report ☐ Follow-up Report

***ADVERSE REACTION DESCRIPTION** (inc. sequence of adverse events, details of rechallenge, interactions)

Time to onset of reaction : ☐ mins/ hours/ days/ months/ years *(please circle)* | Date start of reaction : DD / MM / YYYY | Date end of reaction : DD / MM / YYYY

Reaction subsided after stopping drug / reducing dose : Yes ☐ No ☐ Unknown ☐ ♦N/A (drug continued) ☐

Reaction reappeared after reintroducing drug : Yes ☐ No ☐ Unknown ☐ ♦N/A (not reintroduced) ☐

Extent of reaction : Mild ☐ Moderate ☐ Severe ☐

Seriousness of reaction : Life threatening ☐ | Caused or prolonged hospitalisation ☐ | Caused disability or incapacity ☐ | Caused birth defect ☐ | ♦N/A (not serious) ☐

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(s) :** ♦*N/A: Not applicable*

Product / Generic Name	Dose & Frequency Given	MAL No.	Batch / Lot No.	Therapy Dates		Indication
				Start	Stop	

For Vaccines Only: Vaccine dose (*please circle*) : 1st/ 2nd/ 3rd/ booster/ others _____ Diluent Batch / Lot No. :

Concomitant Drug(s) / Other Vaccine(s) given just prior to AEFI [adverse events following immunisation] *(please state 'NIL' if none)* :

Product / Generic Name	Dose & Frequency Given	MAL No.	Batch / Lot No.	Therapy Dates		Indication
				Start	Stop	

(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 :

revision-01

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.*

ConSERF

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**.*

Report No. *(for official use):*

Information about the person who had the side effect

Name :
*Gender: □ Male □ Female
*Age :

Nationality: □Malaysian □Other:_____
*Ethnicity: □ Malay □ Chinese □ Indian □ Other:_____

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

E.g.: Diabetes, high blood pressure, asthma, allergy to painkiller, or 16 weeks pregnant

Reporter details

Date of report:
Reporter's name:
*Tel. Number :
Email address:

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

Suspected Medicine(s): *(please attach additional sheets if necessary)*

Suspected medicine name *(include MAL number if known)*	Dosage *(e.g. 250mg three times daily)*	Dates: Started	Dates: Stopped	Reason for use
		DD/MM/YY	DD/MM/YY	

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

Other medicine(s) name *(include MAL number if known)*	Dosage *(e.g. 250mg three times daily)*	Dates: Started	Dates: Stopped	Reason for use
		DD/MM/YY	DD/MM/YY	

Information on the side effect(s)

1. * **Date** of side effect(s): a) Reaction started on D D M M Y Y b) Reaction subsided on D D M M Y Y
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

Ver.1.1 (2016)

BORANG PEMANTAUAN KESAN ADVERS RINGAN SUSULAN IMUNISASI

Pindaan-5

Sekiranya anda atau orang yang berada di bawah jagaan anda mengalami kesan advers susulan imunisasi, sila isi borang ini dan kembalikan kepada kakitangan institusi kesihatan tempat vaksin diterima atau yang berdekatan.

Nama klinik/sekolah/lain-lain tempat di mana vaksin diterima: .....

1. Maklumat penerima vaksin:-
   a) Nama: .....
   b) Umur: ..... c) Jantina: ☐ Lelaki ☐ Perempuan
   d) No. telefon: .....
   e) Bangsa: ☐ Melayu ☐ India ☐ Cina ☐ Lain-lain (nyatakan) .....

2. Tarikh vaksin diterima: .....
3. Masa vaksin diterima: .....
4. Kesan advers yang dialami:-

(Tempoh masa berlakunya kesan advers selepas menerima vaksin adalah penting untuk diisi)

Kesan advers (*potong yang tidak berkaitan)	Tandakan √ jika berkaitan	Tempoh masa berlakunya kesan advers selepas menerima vaksin (*potong yang tidak berkaitan)
a. Kesan pada tempat suntikan:		
i) Bengkak	☐	.....minit/jam/hari*
ii) Sakit	☐	.....minit/jam/hari*
iii) Kegatalan	☐	.....minit/jam/hari*
iv) Merah pada tempat suntikan	☐	.....minit/jam/hari*
v) Lain-lain (nyatakan)	☐	.....minit/jam/hari*
b. Demam	☐	.....minit/jam/hari*
c. Ruam/gatal*	☐	.....minit/jam/hari*
d. Kerengsaan (irritability)	☐	.....minit/jam/hari*
e. Kurang selera makan	☐	.....minit/jam/hari*
f. Sakit kepala/pening kepala*	☐	.....minit/jam/hari*
g. Loya/muntah*	☐	.....minit/jam/hari*
h. Sakit otot/badan*	☐	.....minit/jam/hari*
i. Lemah tangan/kaki*	☐	.....minit/jam/hari/minggu*
j. Lain-lain (nyatakan)	☐	.....minit/jam/hari*

5. Adakah penerima vaksin menerima sebarang rawatan di klinik/hospital untuk kesan advers yang dialami?
   ☐ Ya ☐ Tidak
6. Adakah kesan advers tersebut dapat diatasi atau pulih? ☐ Ya ☐ Tidak

7. Maklumat vaksin yang diterima:-
   a) Jenis vaksin
   - ☐ BCG
   - ☐ Hepatitis B, Dos: pertama/kedua/ketiga*
   - ☐ DTaP-IPV-HepB-Hib Dos: pertama/kedua/ketiga/booster*
   - ☐ Pneumokokal, Dos: pertama/kedua/booster*
   - ☐ Measles
   - ☐ Japanese encephalitis, Dos: pertama/kedua
   - ☐ Lain-lain (nyatakan): .....
   - ☐ MMR, Dos: pertama/kedua
   - ☐ Diphtheria & Tetanus
   - ☐ Measles & Rubella
   - ☐ Human papillomavirus, Dos: pertama/kedua*
   - ☐ Tetanus
   - ☐ Polio, oral/suntikan*

   b) Perihal vaksin

<u>Vaksin 1</u>
Jenama vaksin: .....
No. kelompok: .....
Tarikh luput: .....
Bahagian badan yang disuntik: ☐ Lengan ☐ Paha
(jika berkaitan) ☐ Kanan ☐ Kiri

<u>Vaksin 2</u>
Jenama vaksin: .....
No. kelompok: .....
Tarikh luput: .....
Bahagian badan yang disuntik: ☐ Lengan ☐ Paha
(jika berkaitan) ☐ Kanan ☐ Kiri

9. Maklumat pelapor:- ☐ Ibubapa/penjaga ☐ Penerima vaksin ☐ Anggota kesihatan
   a) Nama: .....
   b) No. telefon: .....
   c) Tarikh laporan: .....

Maklumat tambahan bagi anggota kesihatan
d) Jawatan & tempat bertugas: .....
.....
e) Jenis imunisasi: ☐ Rutin ☐ Kempen

Segala maklumat yang dikemukakan adalah sulit dan hanya akan digunakan untuk tujuan memantau kesan advers ringan susulan imunisasi sahaja.

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day | Month | Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day | Month | Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
						☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)						

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

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, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

2

APPENDIX 2: SUMMARY OF EXPEDITED ADR REPORTING REQUIREMENTS TO THE AUTHORITY (TIMELINE FOR ADR/AEFI REPORTING)

Reporter Category	Types of Adverse Reaction	Time Frame for Reporting
Product Registration Holder (PRH)	**Local report**	
	Serious (expected or unexpected) with fatal or life-threatening outcome	As soon as possible, but no later than seven (7) calendar days, after first knowledge by PRH, followed by complete report within eight (8) calendar days, except for AEFIs with fatal outcome. The AEFIs with fatal outcome cases, initial report should be reported within 24 hours after becoming aware of the event. This followed by the assessment from the investigation and other relevant documents within seven (7) calendar days after the initial report.
	Serious, (expected or unexpected) but there are no life-threatening or fatal outcome	As soon as possible but no later than 15 calendar days after first knowledge by PRH
	Non-serious, expected or unexpected	Within 30 calendar days
	Foreign reports	
	Individual case report	Not required on routine basis
	Notification of any emerging safety issue such as new information impacting on risk(s) benefit profile of medicinal product including international regulatory decision or action	No later than three (3) calendar days after first knowledge by PRH
	Withdrawal/suspension of registration in any country due to safety reason	24 hours after first knowledge by PRH

APPENDIX 3: ANNEX FOR PBRER SUBMISSION

I. Product Overview in Malaysia

Date of Submission	DD/MM/YYYY
Submission Number (PBRER Cover Period)	e.g. 1st submission (DD/MM/YYYY – DD/MM/YYYY)
Product Name	
Active Ingredient(s)	
Dosage Form	
MAL Number	
Date of First Registration Approval in Malaysia (DCA Meeting)	DD/MM/YYYY (DCA No. XXX)
International Birth Date (IBD)	DD/MM/YYYY
Product Category	e.g. New drug product / Biologics/ Others
Product Registration Holder (PRH)	
Details of Responsible Person for Pharmacovigilance (RPPV) (name, designation, email, telephone number)	
Approved Indication(s)	

II. Summary of Safety Changes

a) Actions Taken in the Reporting Interval for Safety Reasons

Brief tabulated summary of significant actions related to safety that have been taken in any other countries during the reporting interval, relating to marketing experience by the PRH, or authorities.

<*Suggested format*>

Action(s) taken by	Description of the action(s) taken	Status of the action(s) taken
US FDA	PRH was requested to include liver injury in the Warnings and Precautions section of the US PI.	Updated US PI was approved on DD/MM/YYYY

b) Changes in Reference Safety Information (RSI)

Brief tabulated summary of changes in RSI during the reporting interval.

<*Suggested format*>

Version (Date)	Description of changes	Applicable to Malaysia (Yes/No)
3.0 (DD/MM/YYYY)	Update to the Warnings and Precautions section regarding the risk of heart failure	Yes

c) Action(s) Taken or Planned in Malaysia

State whether or not a specific action has been taken or is planned for Malaysia, pertaining to the actions taken or RSI changes listed above in II(a) and II(b). If any actions are taken in Malaysia, the status of the actions should be listed.

<*Suggested format*>

Type of action/ plan	Details
Safety-related	
Non safety-related	

III. List of Signals Evaluated

To list all signals that were closed (e.g. the evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation, at the end of reporting interval.

The description(s) of the signal evaluations are not to be included.

For Office Use Only	
NPRA Reference Number	
Date Received	
Date Assessed	
Name of Assessor	
Remarks	

APPENDIX 4: ANNUAL SAFETY REPORT FORMAT (ORPHAN MEDICINE)

The information included in the annual safety 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 to contain the following:

i. Introduction

ii. Changes to the PRH's product safety information

iii. Line listing(s) and summary tabulations (see below)

iv. Critical Analysis:

a) A change in characteristics of expected reactions, e.g. severity, outcome, target population;
b) Serious unexpected reactions, placing into perspective the cumulative reports since marketing;
c) Non-serious unexpected reactions;
d) An increased reporting frequency of expected reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence;
e) 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);
f) 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.

v. A review of ongoing clinical study.

vi. Any risk minimisation activities or programmes requested by other authorities relevant to the registered orphan medicine.

vii. A description of the investigation plan for the coming year.

viii. Other information (e.g. information related to effectiveness and late-breaking information)

ix. 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:

i. For drugs, from unsolicited sources:

   a) All domestic, serious ADR;

   b) All domestic non-serious unexpected ADR.

ii. Domestic cases of unusual failure in efficacy;

iii. For drugs, from solicited sources where there is a reasonable possibility that the drug caused the adverse reaction.

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:

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

Summary Tabulations

An aggregate summary for each of the line listings should be presented. 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, is considered suitable.

APPENDIX 5: ISSUE-RELATED SUMMARY REPORT (IRSR) FORMAT

The information requested in an IRSR should contain, but is not limited to the following:

i. Medical definition of the adverse reaction(s) relating to the subject of the report;

ii. Description of the search strategy to retrieve the cases (e.g. from databases);

iii. Detailed summary analysis of the cases (both local and global cases). Information should include, but not be limited to: tabulation of all events; PRH comments on the cases; summary analysis of the temporal relationship between product administration and the occurrence of the events; and summary analysis of possible risk factors and confounding variables;

iv. Local and international patient exposure data using both patient-years and total number of patients exposed, if data are available;

v. A conclusion as to the safety and/or the effectiveness of the product with regards to the occurrence of these events and if applicable, any planned risk minimisation actions or change to the Risk Management Plan, package insert, or label;

vi. In certain instances, additional information may be requested, which would be stipulated during communication with PRH.

APPENDIX 6: TEMPLATE FOR RISK MANAGEMENT PLAN (RMP)/ MALAYSIA-SPECIFIC ANNEX (MSA)

RISK MANAGEMENT PLAN (RMP)
Malaysia-Specific Annex (MSA)

I. Product Overview in Malaysia

Date of Submission	DD/MM/YYYY
MSA Version Number	Current MSA version number e.g. V1
Product Name	
Active Ingredient(s)	
Dosage Form	
MAL Number	
Date of First Registration Approval in Malaysia	
Product Category	e.g. New drug products / Biologics/ Others
Product Registration Holder (PRH)	
Details of Responsible Person for Pharmacovigilance (RPPV) (name, designation, email, telephone number)	
Approved Indication(s)	

II. Changes from Previous RMP Version

Brief summary of significant safety-related changes from the previous RMP submission.

This section may not be applicable for the first RMP submitted post-registration.

III. Summary of Changes to the MSA Over Time

Brief tabulated summary of safety-related changes to the MSA over time.

<Suggested format>

Date of Submission	MSA Version Number	Description of Change
DD/MM/YYYY	V1	First MSA submitted post-registration
DD/MM/YYYY	V2	

IV. Safety Specification: Summary of Safety Concerns

To list the safety concerns in relation to the approved indication(s) in Malaysia.

<Suggested format>

Important identified risks	Heart failure
Important potential risks	Liver injury Peripheral neuropathy
Missing information	Bone fracture

V. Local Pharmacovigilance Plan

To describe the pharmacovigilance activities (routine and/or additional), relevant to the Malaysian context, that are planned or carried out to address the safety concerns.

Routine pharmacovigilance activities are required for all products.

If no additional pharmacovigilance activities are deemed necessary, it should be indicated as ‘nil’.

a) Routine Pharmacovigilance Activities

To describe routine activities that are planned or carried out in Malaysia.

b) Additional Pharmacovigilance Activities by Safety Concern

<Suggested format>

Safety Concerns	Local Pharmacovigilance Activities	Additional Information
Important identified risks		
Heart failure	***Additional:*** PASS [study title]	
Important potential risks		
Liver injury	***Additional:*** Nil	
Peripheral neuropathy	***Additional:*** Nil	
Missing information		
Bone fracture	***Additional:*** Nil	

VI. Local Risk Minimisation Plan

To describe the risk minimisation activities/measures (routine and/or additional), relevant to the Malaysian context, that are planned or carried out to address the safety concerns.

Routine risk minimisation activities are required for all products.

If no additional risk minimisation activities are deemed necessary, it should be indicated as ‘nil’.

a) Routine/Additional Risk Minimisation Activities by Safety Concern

<Suggested format>

Safety Concerns	Local Risk Minimisation Activities	Additional Information
Important identified risks		
Heart failure	***Routine:*** Prescription-only medicine; Labelling in local PI: 'Section 4.4 Special warnings and precautions for use' and 'Section 4.8. Undesirable effects'; Labelling in RiMUP: 'Before you start to use it' and 'Side effects'. ***Additional***: DHPC letter & educational materials	
Important potential risks		
Liver injury	***Routine:*** Prescription-only medicine. Labelling in local PI: 'Section 4.4 Special warnings and precautions for use' and 'Section 4.8. Undesirable effects'; Labelling in RiMUP: 'Before you start to use it' and 'Side effects'. ***Additional:*** Educational materials	
Peripheral neuropathy	***Routine:*** Prescription-only medicine. Labelling in local PI: 'Section 4.4 Special warnings and precautions for use' and 'Section 4.8. Undesirable effects'; Labelling in RiMUP: 'Before you start to use it' and 'Side effects'. ***Additional:*** Educational materials	
Missing information		
Bone fracture	***Routine:*** Nil ***Additional:*** Nil	

VII. <u>Additional Information</u>

To list the RMP documents enclosed in this submission and to provide other comments (if applicable).

If the additional risk minimisation activity includes a Patient Alert/Reminder Card, the following information are required:

Patient Alert/Reminder Card Checklist

No.	Requirements
1	**Product Name**
2	**Active Ingredient**
3	**Dosage form**
4	**Introduction** • This patient alert/reminder card contains important safety information that you need to be aware of before, during, and after treatment with **Product Name**. • Show this card to any doctor, pharmacist, dentist or other healthcare professional involved in your treatment.
5	**Content information** • To be aligned with latest approved package insert.
6	**Warnings and Contraindication** • When to seek immediate attention • Contraindication • Information on pregnancy
7	**Additional Advice:** • Please make sure you also have a list of all your other medicines with you at any visit to a doctor/pharmacist. • Keep this card for ***'X number'*** months after treatment is completed since side effects may occur after your last dose.
8	**Treatment details** (To be filled section): • My name: • My contact no.: • My emergency contact no.: • My Doctor's name: • My Doctor's Clinic contact no.: • Dose regimen: • Start date:
9	**ADR reporting details:** If you notice any side effects, talk to your doctor or pharmacist. You may report any adverse drug reactions directly to the National Pharmaceutical Regulatory Agency (NPRA) at the official website: https://www.npra.gov.my/index.php/en/consumers/reporting/reporting-side-effects-to-medicines-conserf-or-vaccines-aefi-2.html
10	***Additional information (for biologic/biosimilar products only):*** *All ADR reports for biologics/biosimilars should include: Brand name, active ingredient, MAL no. and batch number for traceability purposes.*
11	**Version and month & year of update**

For Office Use Only	
NPRA Reference Number	
Date Received	
Date Assessed	
Name of Assessor	
Remarks	

APPENDIX 7: SAMPLE OF THE PHARMACOVIGILANCE SYSTEM SUMMARY (PVSS)

<Product Holder Details>

<Date>

The Pharmacovigilance (PV) System Summary

To the National Pharmaceutical Regulatory Agency (NPRA),

Summary on the current pharmacovigilance system

<Organisational structure, including PV Unit>
<Brief description on the PV system/database>

We are committed to develop the pharmacovigilance system master file during this transition period, to describe in detail the pharmacovigilance system used by our company in accordance with the requirements stated in Malaysian Guidelines on Good Pharmacovigilance Practices for Product Registration Holders (PRH).

Registered products in Malaysia

<Fill in according to the table below. Please insert "NA" if the product category is unrelated. If the registration is marked as "conditional registration", please state the given condition.>

No	Product Name (As per registered)	Generic Name/Active Ingredient	MAL Number	Special Condition of Registration? (Y/N)	Marketing Status (Marketed/ Not Marketed)
New Drug Product					
1					
2					
3					
Biologics					
1					
2					
3					

Prescription					
1					
2					
3					
Non-Prescription					
1					
2					
3					
Combo Product					
1					
2					
3					

Registered products under current Ministry of Health (MOH) tender

<List down related products and the tender validity>

< Please insert “NA” if this is unrelated>

Registered products under current National Immunization Program

<List down related products and the tender validity>

< Please insert “NA” if this is unrelated>

Registered products categorized as orphan medicine

<List down related products>

< Please insert “NA” if this is unrelated>

Number of Adverse Drug Reaction (ADR)/ Adverse Event Following immunization (AEFI) Reports received over the past 12 months

< The selected 12-month period is specified by the PRH>

Contact detail and curriculum vitae (CV) of RPPV, Local Contact Person (if applicable) and back-up for both (if applicable)

<The responsible person for pharmacovigilance (RPPV)>

And

<The Local Contact Person> (if applicable)

And

< The back-up RPPV and local contact person (if applicable)>

<Note: All the contacts should include full name, tel. no., fax. no., emergency tel. no., email add., designation and mailing address>

Yours sincerely,

(Name)

Designation

APPENDIX 8: TEMPLATE FOR DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

<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; e.g. 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: 5450/5448)
- By facsimile: 03-79567075 using the form available at: https://npra.gov.my/index.php/en/health-professionals/reporting-adr.html
  Or mail to the following address:
  National Pharmaceutical Regulatory Agency (NPRA)
  Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz)
  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)

Designation

Reference

<Any literature references/scientific information sourced>

Below are the documents that have been referred to while preparing this guideline:

1. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module I – Pharmacovigilance Systems and Their Quality Systems - *June 2012*
2. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File (Rev 2) – *March 2017*
3. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module IV – Pharmacovigilance Audits (Rev 1) - *August 2015*
4. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk Management Systems (Rev 2) – *March 2017*
5. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Collection, Management and Submission of Reports of Suspected Adverse Reactions to Medicinal Products (Rev 2) – *July 2017*
6. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module IX – Signal Management (Rev 1) – *October 2017*
7. Health Canada Good Pharmacovigilance Practices (GVP) Guidelines – *August 2013*
8. Health Canada Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products - Guidance Document for Industry – *May 2018*
9. ICH E2C (R2) Guideline: Periodic Benefit-risk Evaluation Report (PBRER) – *December 2012*
10. ICH E2E Guideline: Pharmacovigilance Planning – *November 2004*
11. Malaysia Personal Data Protection Act 2010
12. TGA Pharmacovigilance Responsibilities of Medicine Sponsors – *June 2018*
13. US FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Box Warning Sections of Labelling for Human Prescription Drug and Biological Products — Content and Format – *October 2011*
14. WHO Western Pacific Region Immunization Safety Surveillance Third Edition – *2015*