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National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

MALAYSIAN GUIDANCE DOCUMENT ON VOLUNTARY GOOD PHARMACOVIGILANCE PRACTICES (GVP) INSPECTION

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GLOSSARY

Authority
Drug Control Authority

Corrective Action and Preventive Action (CAPA)
CAPA system is one of the elements of a good Quality Management System. It is a useful tool to implement corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

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.

Individual Case Safety Report (ICSR)
A report of information describing adverse event(s)/reaction(s) experienced by an individual patient.

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 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.

Product Registration Holder (PRH)
The company or corporate or legal entity in the field of pharmaceuticals who has been granted the marketing authorization.

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

ABBREVIATIONS

ADR	Adverse Drug Reaction
CAPA	Corrective Action and Preventive Action
DCA	Drug Control Authority
DHPC	Direct Healthcare Professional Communication
GVP	Good Pharmacovigilance Practices
ICSR	Individual Case Safety Report
JKPPPK	*Jawatankuasa Penilaian Pemeriksaan Premis & Kajian*
NPRA	National Pharmaceutical Regulatory Agency
PBRER	Periodic Benefit-Risk Evaluation Report
PRH	Product Registration Holder
PSMF	Pharmacovigilance System Master File
PV	Pharmacovigilance
PVSS	Pharmacovigilance System Summary
RMP	Risk Management Plan
RPPV	Responsible Person for Pharmacovigilance

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PART 1.0: INTRODUCTION

Good Pharmacovigilance Practices (GVP) Inspection is aimed to ensure that the Product Registration Holders (PRHs) or any parties employed by PRHs that are involved in any pharmacovigilance activities comply with the pharmacovigilance obligations and guidance laid out in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for PRHs, as well as post-registration safety-related requirements imposed by the Authority. As such, this guidance document is to be read together with the current edition of Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for PRHs.

The implementation of GVP Inspection will be done in phases and in the preliminary phase also known as the voluntary phase, PRHs' participation in the programme will be entirely voluntary. This is to allow ample time for PRHs to understand the new pharmacovigilance requirements stipulated in the new guidelines and prepare their pharmacovigilance systems accordingly. The voluntary phase will also provide opportunity for the regulator to identify and address any gaps and challenges in conducting this new activity particularly in this unprecedented pandemic situation before a full-fledged implementation of GVP Inspection in the future.

In view of uncertainty arising from the COVID-19 pandemic, many other national regulatory authorities have moved towards a safer, more flexible, and pragmatic approach of inspection, which is remote inspection without compromising the objectives of inspections. This inspection approach may be continued even after the pandemic, but for different reasons and probably to different degrees. Following similar approach, the National Pharmaceutical Regulatory Agency (NPRA) would adopt this approach and conduct remote inspection during the COVID-19 pandemic and other crisis situations which render on-site inspection not possible. However, NPRA would conduct on-site inspection if deemed necessary.

This guidance document is intended to provide detailed information on the Malaysian voluntary GVP Inspection programme. It also serves as a guide for the PRHs that choose to participate in this programme. The PRHs are required to provide the Pharmacovigilance System Summary (PVSS) and up-to-date Pharmacovigilance System Master File (PSMF) which will be used in the voluntary GVP Inspection.

P1.1 OBJECTIVES

The main aim of the voluntary GVP Inspection is to facilitate PRHs to build and strengthen their pharmacovigilance systems and practice in accordance to the Malaysian Guidelines on GVP.

The objectives of the voluntary GVP Inspection are:

i. To evaluate stakeholders' readiness for GVP inspection;

ii. To identify and gather information on capabilities and challenges faced by PRHs in building compliance towards requirements stipulated in the Malaysian

Guidelines on Good Pharmacovigilance Practices (GVP) for PRHs as well as post-registration safety-related requirements imposed by the Authority;

iii. To test out the feasibility and practicality of the different inspection methods including remote inspection and a hybrid of both remote & on-site inspection;

iv. To strengthen GVP inspection capabilities of inspectors and the PRHs personnel.

P1.2 SCOPE OF VOLUNTARY GVP INSPECTION

i. The aim of voluntary GVP Inspection is to review the overall procedures, systems, personnel, and facilities set in the pharmacovigilance system of a company, and to determine their ability to comply with pharmacovigilance regulatory obligations. However, during a voluntary GVP Inspection, the focus may also be set on product-related pharmacovigilance issues (product-specific activities and documentation), rather than a general system review. Nevertheless, some aspects of the general system may still be examined as part of a product-related inspection.

ii. At this voluntary GVP Inspection stage, Traditional Medicines and Health Supplements (TMHS) products are not included in the programme. However, PRHs are required to operate a pharmacovigilance system [refer to Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for PRHs] to ensure that the safety of the public is being protected.

iii. As mentioned in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for PRHs, the focus of pharmacovigilance inspection will be mainly on Malaysia activities. Pharmacovigilance inspection on global information will be conducted only when necessary.

P1.3 RISK-BASED APPROACH IN VOLUNTARY GVP INSPECTION PLANNING

i. This voluntary GVP Inspection is scheduled in advance through a risk-based approach. A risk-based approach is adapted in the voluntary GVP Inspection programme to make the best use of the resources whilst prioritising public health protection.

ii. The PRHs who are interested in joining the voluntary GVP Inspection programme are required to submit the PVSS, which is a document that briefly describes or summarises the pharmacovigilance system. The PVSS will be used by the Authority for risk-based assessment.

iii. Factors which may be taken into consideration by the Authority when establishing the selection of PRHs to be prioritized for inspection during the voluntary GVP Inspection include (but **not limited to**):

PRHs related factors

a) PRHs with several products on the market in Malaysia;

b) Recent changes in the PRH's organisational structure, such as mergers and acquisitions.

Pharmacovigilance system related factors

a) PRH with engagement of a third party on pharmacovigilance activities (e.g. RPPV and local contact person or reporting of ADR) and/or multiple firms employed to perform pharmacovigilance activities;

b) Recent change of responsible person for PV (RPPV);

c) Changes to the pharmacovigilance safety database(s), including transfer or migrating data;

d) Delegation or transfer of PSMF management;

e) Changes in contractual arrangements, letter of appointment and official document with pharmacovigilance service providers.

Product-related factors

a) Product(s) with large patient exposure in Malaysia;

b) Product(s) with limited alternative in the current market;

c) Product(s) with specific registration condition that require additional monitoring.

P1.4 DECLARATION FORM FOR VOLUNTARY GVP INSPECTION

The PRHs that have been shortlisted based on the risk-based approach will be invited to take part in the voluntary GVP Inspection programme. The PRHs that agree to take part in the programme will sign a declaration form before further arrangements on the GVP Inspection are made. The declaration form serves as a commitment document that allows the inspectors to conduct the inspection (remote/hybrid/on-site), request and review any documents which are required for the exercise of GVP Inspection.

P1.5 METHOD OF VOLUNTARY GVP INSPECTION

The Authority will communicate with PRHs on the selection of GVP Inspection method prior to the inspection. The method of choice will be determined by the Authority. Various factors would be taken into account in determining method of inspection such as the pandemic or other crisis situation, and the complexity of PV system. The

finalized inspection mechanism would be notified to the PRHs by the lead inspector before the inspection.

There are three methods of GVP inspection as below:

a) Remote inspection;
b) Hybrid inspection (combination of remote & on-site inspections); and
c) On-site inspection.

P1.5.1 Remote GVP Inspection

i. This is an off-site GVP Inspection. Remote Inspection includes documentation review and followed by a virtual inspection. Refer P1.6 for Conduct of Voluntary GPV Inspection and P1.6.1 for Flow of Voluntary GVP Inspection.

ii. In addition to sharing documentation as in remote inspection, virtual inspection utilizes technologies such as live or real-time streaming video, screen-sharing, or other means of real-time communication. Virtual inspection may include virtual tour, video communications and interviews.

iii. This approach can only be taken if interviews of relevant staff and review of documentation, including safety database, source documents and PSMF could be done via remote access.

iv. PRH is expected to arrange the platform/logistics for the remote inspection and to communicate this arrangement with the lead inspector.

P1.5.2 Hybrid GVP Inspection

i. The Authority may also opt for a hybrid inspection which incorporates both remote and on-site inspection if the remote inspection alone fails to meet the objective of the inspection. Refer P1.6 for Conduct of GPV Inspection and P1.6.1 for Flow of Voluntary GVP Inspection.

ii. If on-site inspection is required, the arrangement of the on-site inspection will be communicated to the PRHs prior to the inspection date.

iii. During on-site inspection, PRHs are expected to provide working space that enables social distancing, and implement other safety measures according to the latest guidelines or Standard Operating Procedures issued by the government.

P1.5.3 On-site GVP Inspection

i. Based on the risk assessment conducted, related to the size of the company/premise, complexity of the PV system/process and etc., the

Authority may decide to perform an on-site GVP Inspection. Refer P1.6 for Conduct of GPVI and P1.6.1 for Flow of GVP Inspection.

P1.6 CONDUCT OF VOLUNTARY GVP INSPECTION

i. The PRHs would sign a declaration form upon agreeing to join the GVP Inspection.

ii. During preparation for the inspection, an inspection plan is established. The inspection plan will depend on the scope and method of inspection intended. Then, the inspection will be conducted.

iii. Any party carrying out pharmacovigilance activities in whole or in part, in conjunction with the PRHs may be inspected, in order to confirm their capability to support the PRH's compliance with pharmacovigilance obligations. Generally, such inspections will be arranged through the PRHs as part of an overall pharmacovigilance inspection.

iv. The PRHs have the responsibilities in relation to inspections, **including but not limited to** the following:

a) Submit the updated PSMF (with annexes) and any additional data requested by the inspector within the given timeline, for the purpose of reviewing the pharmacovigilance system before the inspection is carried out;

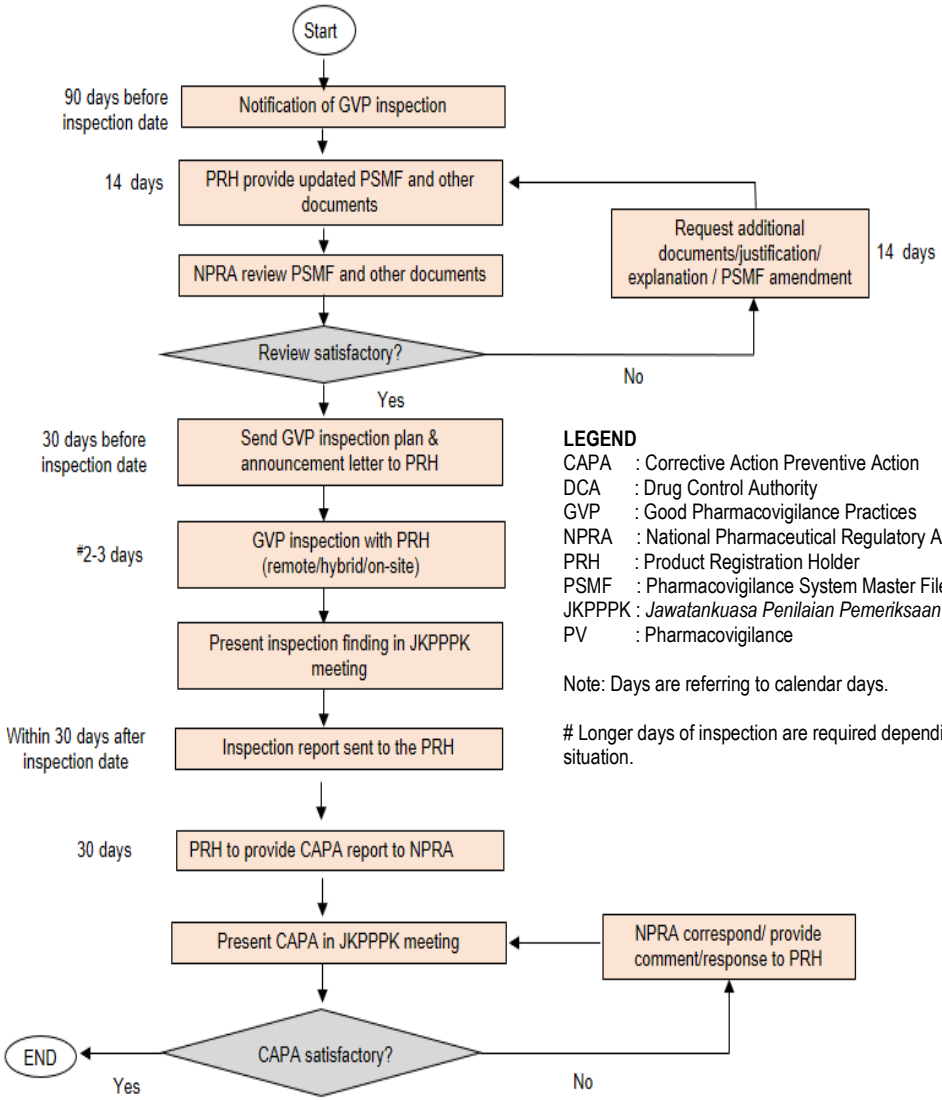
b) To ensure the RPPV and local contact person (if applicable) and the relevant personnel involved are present and available during the inspection for interviews or clarification of issues identified;

c) To make available to the inspector any information, documentation and record required during the inspection;

d) To propose the corrective and preventive action plans to the inspector within the given timeline and implement appropriate and timely measures to address the findings observed following the inspection.

P1.6.1 Flow of the GVP Inspection

Diagram below shows the flow of a voluntary GVP inspection:



LEGEND

CAPA : Corrective Action Preventive Action
DCA : Drug Control Authority
GVP : Good Pharmacovigilance Practices
NPRA : National Pharmaceutical Regulatory Agency
PRH : Product Registration Holder
PSMF : Pharmacovigilance System Master File
JKPPPK : *Jawatankuasa Penilaian Pemeriksaan Premis & Kajian*
PV : Pharmacovigilance

Note: Days are referring to calendar days.

Longer days of inspection are required depending on the situation.

P1.6.2 Announcement of the GVP Inspection

i. The inspections will be notified in advanced (approximately 90 calendar days), to ensure the availability of relevant individuals for the inspection. The inspection plan and official announcement letter will be sent to participating PRHs approximately 30 calendar days before inspection date.

ii. For remote inspection, more documentation will be requested in advance of the inspection.

P1.6.3 Opening Meeting

i. An opening meeting must take place between the inspector and the inspectee before the start of the pharmacovigilance inspection.

ii. The purposes of an opening meeting include: to introduce the inspector(s) and the inspectee(s), to identify the delegation of activities in Pharmacovigilance system among the inspectee(s), to explain the regulatory framework for the conduct of the inspection, to review the scope and objectives of the inspection, to provide a short summary of the methods and procedures to be used in the inspection, and to clarify the inspection plan, if necessary.

P1.6.4 Conduct of the GVP Inspection

i. The inspection activities should have been communicated via the inspection plan prior to the inspection. However, the inspector(s) may adjust the plan during the inspection to ensure that the objectives are achieved.

ii. Information should be collected through examination of computers (if applicable), electronic systems and databases (if applicable), relevant documents and records with direct access, interviews, and observation of activities to fulfill the inspection objective(s).

iii. If access to records or copying of documents is refused for any reason or there is any withholding of documents and records or denial of access to areas to which the inspector has legal access, these refusals should be justified, documented, and included in the inspection findings.

iv. If there are problems encountered with communication during the conduct of the inspection, e.g. internet connection problems, the inspectors will consider to adapt the schedule or even prolong the days of the inspection.

v. No recordings are allowed throughout the inspection process.

vi. Generally, a pharmacovigilance inspection should **at least** cover the following elements, as appropriate:

Individual case safety reports (ICSRs)

a) The collection and receipt of ICSR. It should include all types of sources (including line-listing from the Authority), sites and departments within the pharmacovigilance system;

b) The assessment of the ICSR. The mechanisms for obtaining and recording reporter assessment, company application of event terms, seriousness, expectedness and causality;

c) The follow-up and outcome recording. For example, the outcome of pregnancy exposure cases and medical confirmation of consumer reported cases;

d) The reporting of ICSR to the Authority according to the requirements and time frame;

e) Record keeping and archiving of ICSRs.

Periodic Benefit-Risk Evaluation Reports (PBRERs)
(If applicable)

a) The timeliness of submission to the Authority;

b) The formatting according to requirements;

c) Appropriately address safety topics with relevant analysis and actions;

d) The completeness and accuracy of the data included and appropriateness of decisions relating to the data that are not included.

Safety evaluation

a) Timely identification and provision of complete and accurate data to the Authority when responding to the data requests;

b) The implementation of RMP and other safety commitments that have been agreed;

c) The implementation of approved changes to safety communications and product information, e.g. variation, DHPC, including internal and external distribution/publication;

d) Appropriate analysis methodology on signal detection and the use of relevant sources of information for signal detection;

e) Appropriateness of investigations and follow-up actions related to safety evaluation.

Pharmacovigilance system

a) The roles and responsibilities of PRHs related to the pharmacovigilance system;

b) The accuracy, completeness, and maintenance of the PSMF;

c) The roles and responsibilities of the RPPV and local contact person (if applicable);

d) The contractual agreements/letter of appointment/official document with all relevant parties must be able to reflect responsibilities in fulfillment of pharmacovigilance activities and are adhered to;

e) The quality and adequacy of training, qualifications, and experience of staff.

P1.6.5 Closing of the GVP Inspection

i. At the end of the inspection, there would be a closing meeting between inspector(s) and inspectee(s). The inspector(s) should have reviewed all findings and reported the non-compliance and/or deficiencies in the inspected pharmacovigilance system.

ii. The result of the inspection should be clearly delivered verbally and understood by the inspectee(s) and appropriate management board during the closing.

P1.6.6 Reporting after the GVP Inspection

i. The inspection report should be delivered (via email and/or letter) to the inspectee after last received of documents and/or records submitted to the inspector related to the pharmacovigilance inspection.

ii. Generally, the inspection report will be issued within 30 calendar days from the last day of the inspection or from the last received of documents and/or records submitted to the inspector related to the pharmacovigilance inspection.

iii. The inspection report should describe the method and scope of the GVP Inspection. The finalized pharmacovigilance inspection plan with brief explanation on any deviation to the previously agreed inspection plan due to unforeseen circumstances during actual inspection would be attached in the report as well.

iv. The most important part of the report is the description of the inspection findings. The inspector should describe each of the finding in detail. The

findings will be presented to the *Jawatankuasa Penilaian Pemeriksaan Premis & Kajian* (JKPPPK).

v. All reported findings should be identified with reference to specific requirements of the standard(s) or other related documents. The names and titles of persons interviewed during the inspection and the details of the inspected organisation should be documented.

vi. During this voluntary phase, the GVP Inspection report will state and detail the findings without providing any classification. The classification of the findings is for the Authority's internal use only and is done according to the severity of the findings noted during inspections as shown in the Appendix 1.

vii. All findings detected during this voluntary GVP Inspection will be kept confidential and the participating PRHs will not be identified in any presentation or publication resulting from the inspections.

viii. During this voluntary stage of GVP Inspection, only Corrective Action Preventive Action (CAPA) reports are required from the PRHs in relation to the findings of the inspection. No regulatory action is expected to be taken.

P1.6.6.1 Inspection follow-up

i. The inspectee(s) is requested to respond to all findings made, with corrective actions. Within the requested time frame, the inspector(s) should receive responses from the inspectee(s) and assess the corrective actions.

ii. The CAPA should be provided by the PRHs within a defined time period of 30 calendar days after receiving the inspection report.

iii. The CAPA plan proposed by the inspectee(s) will be reviewed by JKPPPK.

iv. Based on the pharmacovigilance inspection report, the JKPPPK will make the decision on the corrective and preventive action plan proposed by the inspectee(s).

v. If the CAPA are assessed as not satisfactory, additional actions would be requested from the inspectee(s). The inspector(s) will continue to follow-up until the CAPA plan is complete.

APPENDIX 1: THE CLASSIFICATION OF THE FINDINGS

Grading	Details
Critical	A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines. Deficiencies classified as critical may include a pattern of deviations classified as major. A critical deficiency also occurs when a PRH is observed to have engaged in fraud, misrepresentation or falsification of data.
Major	A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines. Deficiencies classified as major may include a pattern of deviations classified as minor.
Minor	A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients. A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.
Comment	Such findings might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

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

1. EMA Guideline on Good Pharmacovigilance Practices (GVP) Module III – Pharmacovigilance inspections (Rev 1) – *September 2014.*
2. EMA Remote Pharmacovigilance Inspections of MAHs During a Crisis Situation - Points to consider – *October 2020.*
3. UK MHRA Guidance for industry on MHRA's expectations for return to UK on-site inspections – *March 2021*.
4. TGA Pharmacovigilance Inspection Program: Guidance for Medicine Sponsors – *September 2017*
5. NPRA Frequently asked questions on Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) inspections by National Pharmaceutical Regulatory Agency (NPRA) during Covid-19 pandemic – *August 2021*.