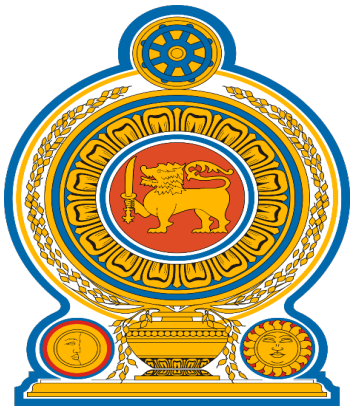

# GUIDELINE ON PHARMACOVIGILANCE SYSTEM MASTER FILE

JANUARY 31, 2022

NATIONAL MEDICINE REGULATORY AUTHORITY
Norris Canal Rd, Colombo 01000, Sri Lanka

CONTENTS

## 1. INTRODUCTION

The legal requirement for marketing authorisation holders (MAHs) to maintain and make available upon request a pharmacovigilance system master file (PSMF) was a requirement of the regulations made under the NMRA Act No 05 2015.

A Pharmacovigilance System Master File (PSMF) is a document describing the pharmacovigilance system used by the MAH with respect to one or more authorized medicinal products

## 2. OBJECTIVES

Through the production and maintenance of the PSMF, the MAH and the Qualified Person for Pharmacovigilance (QPPV) should be able to:

- fulfil the supervisory responsibilities of the QPPV;
- gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
- confirm aspects of compliance in relation to the system
- obtain information about deficiencies in the system, or non-compliance with the requirements;
- obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.
- contribute to the appropriate planning and conduct of audits by the MAH

The use of this information should contribute to the appropriate management of and improvement(s) to the pharmacovigilance system.

The requirements for submission of a summary of the MAH's pharmacovigilance system, provision of the content of PSMF and the history of changes to the NMRA should enable the appropriate planning and effective conduct of inspections by the Authority, based on a risk assessment approach.

## 3. SUMMARY OF THE APPLICANT'S PHARMACOVIGILANCE SYSTEM

Summary of the applicant's Pharmacovigilance system is to be included in the marketing authorization application.

Shall include the following elements:

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance;
- The contact details of the qualified person;

- A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities;
- A reference to the location where the PSMF for the medicinal product is kept and its unique number assigned by the NMRA

## 4. LOCATION, REGISTRATION AND MAINTENANCE

PSMF shall be located either at the site where the main pharmacovigilance activities are performed or at the site where the QPPV operates.

MAH should submit PSMF to the NMRA according to the content described in this guidance to get registration of PSMF. The NMRA keeps the records and assign unique Reference number for the each PSMF.

The PSMF should be written in English, legible, complete, succinct, accurate, reflect the current system in place and provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving. Furthermore, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements

In addition, the MAH shall continue to ensure that the information given in the PSMF about the QPPV, name and contact details (telephone, fax number, postal address and email address) and PSMF location information are up to date. Upon a change in such information, the MAH shall inform the NMRA immediately and not less than 30 Calendar days.

## 5. THE REPRESENTATIONS OF PHARMACOVIGILANCE SYSTEMS

As a general rule, the PSMF shall describe the pharmacovigilance system for the medicinal products of the MAH. A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

The following circumstances may also apply:

- Where a **single MAH wants to establish more than one pharmacovigilance system** e.g. specific system for particular types of products (e.g. vaccine, biologicals, and new chemical entities):
  - each such system shall be described in separate PSMF.

- those file shall cumulatively cover all medicinal products of the MAH for which a marketing authorization has been issued.
- a list of all PSMFs held by the same MAH shall be provided in the each PSMF annex; this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).

- Where a **pharmacovigilance system is shared by several MAHs** (only applicable for subsidiary companies):
  - each MAH is responsible for ensuring that a PSMF exists to describe the pharmacovigilance system applicable for its products.
  - it is advised that the partners agree on how to mutually maintain the relevant sections within their own PSMFs.
  - accessibility of the PSMF to all the applicable MAH(s), and its provision to NMRA should be defined in written agreements.
  - It is vital that MAH(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.
  - For a particular product(s) the MAH may delegate through written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the MAH is responsible. In this case the PSMF of the MAH may cross refer to all or part of the PSMF managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the MAH and the authorities. The MAH should be able to assure the content of the referenced file(s) in relation to the pharmacovigilance system applicable to their product(s).
- When **delegating any activities concerning the pharmacovigilance system and its master file**,
  - the MAH retains ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to NMRA.
  - 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.
- **For foreign MAHs with operating office/branch in Sri Lanka**, the EU/global PSMF (following the EMA format) should reflect the pharmacovigilance system on global level. In addition, PSMF Sri Lanka Annex containing country specific content for the pharmacovigilance system in Sri Lanka should be available and maintained as appropriate. When the company is to submit PSMF; both the EU/global PSMF of the foreign MAH and the PSMF Sri Lanka annex should be submitted except otherwise is requested by the NMRA.

  This local annex should include the following:

1. The contact details, qualification, CV and job description of the Local Safety Responsible (LSR)
2. The lists of contracts and agreements relevant to pharmacovigilance in Sri Lanka.
3. List of Pharmacovigilance- relevant SOPs used on national level
4. List of Pharmacovigilance performance indicators and their current results on national level over the past year.
5. List of pharmacovigilance audit and their findings for company office in Sri Lanka over the past 5 years.
6. List(s) of products authorized/ under authorization in Sri Lanka covered by the pharmacovigilance system, indicating which of them have additional risk minimization measures and/ or additional pharmacovigilance activities.

- **For foreign MAH which is represented at the NMRA through its agent/ importer/ distributer and gave no operating office/branch in Sri Lanka**, the EU/global PSMF (following the EMA format) should reflect the pharmacovigilance system on global level. In addition, the agent/ importer/ distributer in Sri Lanka should have and maintain a PSMF (according to the PSMF content highlighted below) providing description of its pharmacovigilance system in integration with the MAH pharmacovigilance system and according to the Safety Data Exchange Agreement (SDEA) in place between both parties. When the company is to submit PSMF; both the EU/global PSMF of the foreign MAH and the PSMF of the agent/ importer/ distributer in Sri Lanka should be submitted except otherwise is requested by the NMRA.

## 6. ACCESSIBILITY OF THE PSMF AND SUBMISSION TO THE NMRA

- The PSMF shall be kept up to date and be permanently available to the QPPV.
- It shall also be permanently available for inspection, at the site where it is kept, irrespective of whether the inspection has been notified in advance or is unannounced. The MAH must submit the copy 14 days at the latest after receipt of the request from the NMRA. The PSMF should be submitted in a readable electronic format or clearly arranged printed copy.

  In the situation where the same PSMF is used by more than one MAH (where a shared pharmacovigilance system is used by subsidiary companies) the concerned PSMF should be accessible to each, as any of the applicable MAHs shall be able to provide the file to the NMRA within the timeline stated above, upon request

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- The submission of PSMF may be requested on an ad hoc basis, particularly if a new or major change to pharmacovigilance system is being implemented, or if product specific safety concerns or compliance issues with pharmacovigilance requirements have been identified.
- In specific circumstances where deemed necessary, the NMRA may request submission of the PSMF for review and/or conduct of pre-authorization pharmacovigilance inspections before a marketing authorization is approved. This request is made with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorization application.

  To decide on such request, the following aspects shall be considered during the validation phase and/or early during the assessment phase:

  – the applicant has not previously operated a pharmacovigilance system within the country;
  – the applicant has not previously submitted the PSMF to the NMRA or is in the process of establishing a new pharmacovigilance system;
  – the applicant had major changes in its organization, such as mergers and acquisitions or in its pharmacovigilance system
  – previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant has a poor history or culture of compliance. If the applicant/HCR has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorization pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorization is granted;
  – due to product-specific safety concerns, it may be considered appropriate to examine the applicant ability:
    a) to implement product specific risk-minimization activities; or
    b) to meet specific safety conditions which may be imposed; or
    c) to manage routine pharmacovigilance for the product of concern (e.g., anticipated significant increase in adverse reaction reports when compared to previous products).

If the outcome of the PSMF review/pre-authorization inspection raises concerns about the applicant ability to comply with the requirements laid down in the regulations, the following recommendations may be considered:

– non approval of marketing authorization application;
– a re-inspection prior to approval of marketing authorization to confirm that critical findings and recommendations have been addressed;

- granting of the marketing authorization with the recommendation to perform an early post-authorization pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the NMRA routine programme of pharmacovigilance inspections;
- imposition of safety conditions to the marketing authorization;

**7. PSMF CONTENT**

The PSMF shall include documents to describe the pharmacovigilance system; the content of the PSMF should reflect the global availability of safety information for medicinal products authorized in Sri Lanka. The main principle for the structure of the content of the PSMF is that primary topic sections contain information that is fundamental to the description of pharmacovigilance system.

PSMF Cover Page should include:

- The unique number assigned by the NMRA
- The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
- The name of other concerned MAH(s) (sharing the pharmacovigilance system).
- The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system)
- The date of preparation / last update

**7.1 PSMF section on qualified person responsible for pharmacovigilance (QPPV)**

The information relating to the QPPV, and back-up provided in the PSMF shall include:

- job descriptions of the QPPV with responsibilities guaranteeing that he/she has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;
- a summary curriculum vitae with the key information on the role of the QPPV,
- contact details; including name, postal address, telephone, fax and e-mail and represent the usual working address of the QPPV
- details of back-up arrangements to apply in the absence of the QPPV
- The list of tasks that has been delegated by the QPPV and to whom these have been delegated

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance.

If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

**7.2 PSMF section on the organizational structure of the MAH**

A description of the organizational structure of the MAH relevant to the pharmacovigilance system including the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations The PSMF shall describe:

- Diagrams showing the organizational charts and the position of the QPPV in the organization may be particularly useful; the name of the department or third party should be indicated
- The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorization study management, and management of safety variations to product particulars.

Delegated activities

- Description of the activities and/or services subcontracted by the MAH in any country relating to the fulfilment of pharmacovigilance obligations should be provided.
- List/table to show the parties involved, the roles undertaken and the concerned product(s) and territories, including: **service providers** (e.g. medical information, auditors, patient support programme providers, study data management, etc.), **commercial arrangements** (distributors, importers/ agents, licensing partners, co-marketing etc.) and other **technical providers** (hosting of computer systems etc.).
- Individual contractual agreements shall be made available at the request of NMRA or during inspection and audit and the list provided in the Annexes.

**7.3 PSMF Section on the sources of safety data**

- The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorized in Sri Lanka. This should include medical information sites as well as affiliate offices.
- Flow diagrams indicating
  - Inflow of adverse reaction reports and safety information
  - Description of the stages involved in the processing of ICSRs including the timelines for submission to regulatory authorities including the NMRA
  - Outflow of safety data to regulatory authorities including the NMRA

- List of sources of safety data including any studies, registries, surveillance or support programmes sponsored by the MAH through which ICSRs could be reported.
  The list should be comprehensive for products authorized in the Sri Lanka, irrespective of indication, product presentation or route of administration. The list should describe, on a worldwide basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organized per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex. Such list will support inspection, audit and QPPV oversight.

**7.4 PSMF section on computerized systems and databases**

Description of the location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the PSMF in such a way that the extent of computerization within the pharmacovigilance system can be understood.

The validation status the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance should be included in summary, and the nature of the documentation available described.

For paper based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

**7.5 PSMF section on pharmacovigilance processes**

- A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects shall be included in the PSMF:
  - Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc;
  - Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;

- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
- PBRER scheduling, production and submission, if applicable
- Communication of safety concerns to consumers, healthcare professionals and the NMRA;
- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications

In each area, the MAH should be able to provide evidence of a system that supports appropriate and timely decision making and action.

- A list of specific procedures and processes related to the pharmacovigilance activities, as well as interfaces with other functions including, but are not limited to, the roles and responsibilities of the QPPV, responding to NMRA requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. This list (in the Annexes), 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.

**7.6 PSMF section on pharmacovigilance system performance**

The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the **targets** and monitoring methods (**metrics**) applied and contain as a minimum:

- An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by authorities regarding the quality of ICSR reporting, PSURs or other submissions
- An overview of the timeliness of PBRER reporting to NMRA in Sri Lanka (the annex should reflect the latest figures used by the MAH to assess compliance);
- An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and NMRA deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.

A list of performance indicators must be provided in the Annex to the PSMF alongside the **results of (actual) performance measurements** over the past year.

**7.7 PSMF section on quality system**

A description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance. This shall include:

Document and Record Control

A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents

Procedural documents

- A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc), the applicability of the various documents at global, regional or local level within the organization, and the controls that are applied to their accessibility, implementation and maintenance.
- Information about the documentation systems applied to relevant procedural documents under the control of third parties.

Training

Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports and individual whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, telephone operators, receptionists, medical information, sales and marketing, regulatory affairs and legal affairs.

The PSMF should provide:

- description of the resource management for the performance of pharmacovigilance activities: the organizational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities,
- A description of the training organization in relation to the personnel and site information;
- A summary description of the training concept, planning including a reference to the location training files.

- Updated training materials, training plan and evidence of training (training records) should be provided including assessment of the effectiveness of the training programmes as an Annex in the PSMF

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 maintained in the annex. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of local distributers, service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the pharmacovigilance obligations, and cover a rolling 5 year period.

The PSMF shall also contain a note associated with any audit where significant (major or critical) findings are raised and to provide a brief description of their corrective and/or preventative action(s), 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). In case corrective and preventative action plan(s) have not yet been agreed for a particular audit or finding, the PSMF should include the note required and stating that "corrective and preventative action plan(s) are to be agreed".

In the annex, in the list of audits conducted, those associated with unresolved notes in the PSMF, should be identified. The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified. The addition, amendment or removal of the notes must therefore be recorded in the logbook.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

**7.8 Annex to the PSMF**

An annex to the PSMF shall contain the following documents which shall be presented with the following headings and, if hardcopy, in the order outlined below:

Where there is no content for an Annex, it should simply be described as 'unused' in the indexing so the recipients of the PSMF are assured that missing content is intended. In this cases, the Annexes that are provided should still be named according to the format described below WITHOUT reordering.

The qualified person responsible for pharmacovigilance, Annex A

- The list of tasks that have been delegated by the QPPV, or the applicable procedural document
- The curriculum vitae of the QPPV and associated documents
- Contact details supplementary to those contained, if appropriate

The Organisational Structure of the MAH, Annex B

- The lists of contracts and agreements

Sources of safety data, Annex C \

- Lists associated with the description of sources of safety data e.g. affiliates and third party contacts

Computerised systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

- Lists of procedural documents

Pharmacovigilance System Performance, Annex F

- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

Quality System, Annex G

- Audit schedules
- List of audits conducted and completed

Products, Annex H

- List(s) of products covered by the pharmacovigilance system
- Any notes concerning the MAH per product

Document and Record Control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself.

**7.9 Logbook and history of changes**

- All changes to the PSMF must be recorded in a descriptive way (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.
- The QPPV should always be kept informed of such changes as well.
- The history of changes in each related Annex (e.g. product list, standard operating procedure list and compliance figures) should also be regularly updated.
- The superseded versions of such content may be managed outside of the PSMF content itself and made available to the Authority if requested. As a basis for audit and inspections, 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.
- MAH 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.

## 2 REFERENCES

1. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf

## 3 APPROVAL AND REVIEW DETAILS

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|---|---|
| Next Review Date | |