REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

Lebanese Guideline on Good Pharmacovigilance Practices (LGVP)

Module II

Pharmacovigilance System Master File (PSMF) and Pharmacovigilance Sub-System File (PSSF)

Draft finalized by the Pharmacovigilance Working Group, Ministry of Public Health	June, 2023
Draft agreed by the Pharmacovigilance expert consultant	August, 2023
Draft adopted by the Quality Assurance for Pharmaceutical Products Program, Ministry of Public Health	September, 2023
Released for consultation	November, 2023

Table of content

Module II - Pharmacovigilance System Master File (PSMF) and Pharmacovigilance Sub-System File (PSSF)

List of Abbreviations

ICSR: Individual Case Safety Report

KPI: Key Performance Indicator

LSR: Local Safety Responsible

MAH: Marketing Authorization Holder

PSMF: Pharmacovigilance System Master File

PSSF: Pharmacovigilance Sub-System File

PSUR: Periodic Safety Update Report

QPPV: Qualified Person for Pharmacovigilance

SmPC: Summary of Product Characteristics

SOP: Standard Operating Procedures

List of Tables

List of Figures

This Module is divided into three parts:

- **Part 1:** Module organization and terminology;
- **Part 2:** Pharmacovigilance System Master File (PSMF) requirements for national Marketing Authorization Holders (MAHs)/applicants in Lebanon;
- **Part 3:** National Pharmacovigilance Sub-System File (PSSF) and Global PSMF requirements for multinational MAHs/applicants in Lebanon;

Part 1. Module organization and terminology

This part of the Module delivers preliminary remarks designed to offer clarifications on specific terminology and concepts that will be employed consistently throughout the Module. This is done in the aim to facilitate a seamless comprehension of the module's organization and content.

1.II.1. Module organization

- Part 1: "Module organization and terminology": The definitions and terminology introduced in this part of the Module shall be uniformly adopted and applied throughout the entirety of the Module;
- Part 2: "Pharmacovigilance System Master File (PSMF) requirements for national MAHs/ applicants in Lebanon": This part of the Module covers the requirements for multinational MAHs/applicants, for the establishment and submission of the PSMF;
- Part 3: "National Pharmacovigilance Sub-System File (PSSF) and Global PSMF requirements for multinational MAHs/applicants in Lebanon: This part of the Module covers the global requirements for multinational companies for the establishment of the PSMF, as well as the specific requirements for the PSSF with a dedicated emphasis on activities and operations conducted within the country.

1.II.2. Terminology

Within the context of this Module and specifically for Lebanon, the below definitions are exclusively intended for use and relevance.

❖ According to the decree 571/2008 (https://www.moph.gov.lb/Laws/download_file/1191) with regard to the imported pharmaceutical products, the main responsible parties of the product are either the drug manufacturer or the MAH or the Applicant for Certificate.

- **Marketing Authorization Holder (MAH):** The MAH for a drug is the entity or organization that holds the legal responsibility for the drug's marketing authorization in a specific country or region. They are responsible for ensuring compliance with regulatory requirements, and pharmacovigilance.
- **Applicant for Marketing Authorization:** The Applicant for marketing authorization for a drug is the entity or organization that applies to the regulatory authorities seeking approval to market and distribute a drug in a specific country or region. They are responsible for submitting the necessary documentation, including clinical trial data, safety and efficacy information, and manufacturing details, to demonstrate the drug's quality, safety, and effectiveness.

The difference between the Applicant for marketing authorization and the MAH lies in their roles and responsibilities.

❖ The terms "Multinational MAH" and "National MAH" are not standard regulatory terms but can be understood based on their context in the pharmaceutical industry:

- **Multinational MAH/Applicant:** A Multinational MAH is a pharmaceutical company or organization that holds MAs for a specific drug in multiple countries or regions across the world. They have obtained approval from regulatory authorities in various countries, allowing them to market and distribute the drug in those approved markets.
- **National MAH/Applicant**: A National MAH is a pharmaceutical company or organization that holds the marketing authorization for a drug in a single country (Lebanon). They have received approval from the regulatory authority of that specific country (Lebanon), allowing them to market and distribute the drug exclusively within its borders. To note that national MAHs can also export to regional countries but not globally.

The difference between a Multinational MAH and a National MAH lies in the geographic scope of their operations:

- **Scope of a Multinational MAH/Applicant:** A Multinational MAH operates on a global scale, with marketing authorizations secured in multiple countries. This means that a Multinational MAH can commercialize the same drug in several different regions simultaneously, facilitating a broader market reach and potentially greater sales opportunities.
- **Scope of a National MAH/Applicant:** A National MAH operates within one country (Lebanon), so it tends to focus on marketing and distributing drugs within Lebanon, dealing with the regulatory

requirements and specific Lebanese market conditions. To note that national MAHs can also export to regional countries but not globally.

- **Scientific office**: A Scientific Office is essentially a representative office of a multinational pharmaceutical company which manufactures pharmaceutical products.
  The scientific office, often referred to as the Scientific Affairs or Medical Affairs department, is a specialized division within the company that provides scientific, technical and marketing information regarding the company's products.

- **Drug distributor ("Local Agent" in Lebanon):** In the pharmaceutical industry, a drug distributor, also known as a pharmaceutical distributor or wholesale distributor, is an intermediary entity that plays a significant role in the supply chain of pharmaceutical products. The primary function of a drug distributor is to procure pharmaceutical products from manufacturers and then distribute them to various healthcare providers, including pharmacies, hospitals, clinics, and other authorized healthcare facilities. In Lebanon, the drug distributor is also the marketing authorization applicant.

- **Qualified Person for Pharmacovigilance (QPPV):** A QPPV is an individual within a pharmaceutical company who is responsible for the safety of the pharmaceutical products marketed by that company. The QPPV is responsible for establishing and maintaining the MAH's pharmacovigilance system, ensuring compliance with legal requirements, and influencing the performance of the quality system.

- **Local Safety Responsible (LSR):** In addition to the global QPPV, multinational MAHs are required to nominate a local safety person, the LSR, at the national level in the country they intend to operate in. A LSR, usually known as "local QPPV" in Lebanon, is an individual within the pharmaceutical company who is responsible for overseeing pharmacovigilance activities and compliance with local regulatory requirements in a specific geographic region or country.
  A QPPV has global PV system responsibilities, whereas a LSR bears responsibility for the local PV system.

- **PSMF:** The Pharmacovigilance System Master File (PSMF) is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more medicinal products authorized for use in a specific country.

- **PSSF:** Multinational MAH(s)/Applicant(s) conduct their pharmacovigilance activities in affiliate countries as a part or a sub-system of its global pharmacovigilance system and integrate with it.

  For these multinational MAHs/Applicants, the National Pharmacovigilance Sub-System File (PSSF) describes the key elements of pharmacovigilance activities in Lebanon, and includes information and documents to describe the pharmacovigilance sub-system at the national level.

1.II.3. Pharmacovigilance System and Sub-System File in Lebanon: Entities, Roles, and Requested Documents

The below diagram (Figure 1) offers a clear and comprehensive illustration of the distinct entities involved in pharmacovigilance operations, with a specific distinction between two categories of MAH/Applicants: National and Multinational.

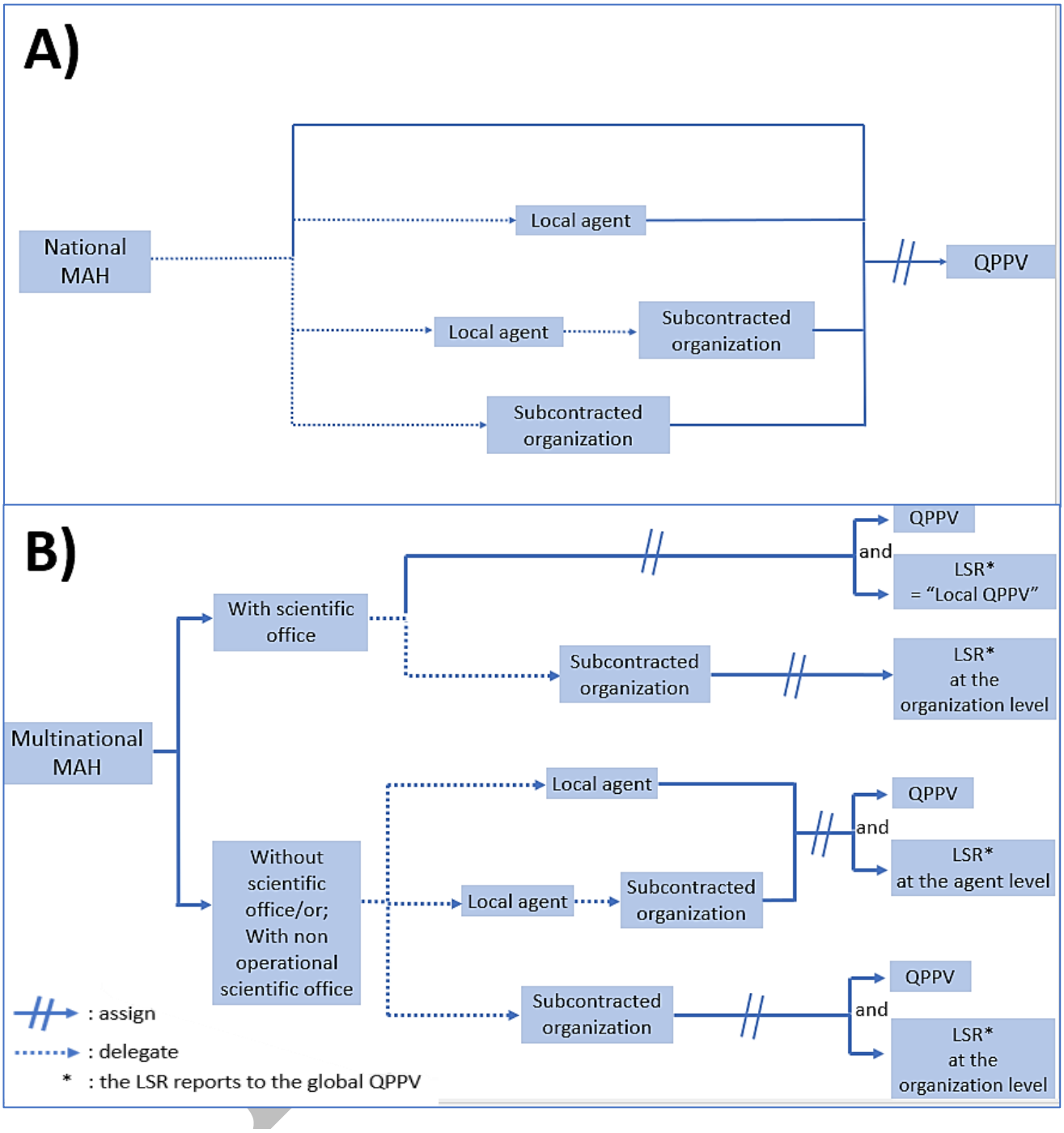

Figure 1: Representation of MAHs

115

116

117

***Legend**:*

- *A national MAH may directly handle its PV activities, or delegate its PV activities to a local agent, or to a local agent who in turn subcontracts these activities to a 3rd-party organization ("Subcontracted organization") where a three-party contract between the MAH, the local agent and the 3rd party is then considered. The MAH may also directly subcontract its PV activities to a "Subcontracted organization"*
  In all cases it must assign a QPPV to oversee its PV activities in Lebanon (Figure 1-A)..

- *A multinational MAH with a scientific office in Lebanon may directly handle its PV activities, or subcontract them to a 3rd-party organization ("Subcontracted organization").*
  In both cases it must assign a QPPV residing at the country of headquarters to oversee its global PV system, along with a LSR residing in Lebanon to represent it at the appropriate level with regard to PV activities (Figure 1-B).

- *A multinational MAH with a non-operational scientific office, or without a scientific office in Lebanon may delegate its PV activities to a local agent. The local agent may in turn subcontract these activities to a 3rd-party organization ("Subcontracted organization"), where a three-party contract between the MAH, the local agent and the 3rd party is then considered.*
  The MAH may also subcontract PV activities directly to a 3rd-party organization ("Subcontracted organization".
  In all cases it must assign a QPPV residing in the country of headquarters to oversee its global PV system, along with a LSR (residing in Lebanon) to represent it at the appropriate level with regard to PV activities (Figure 1-B).
- *To note that the MAH should retain full responsibility in ensuring the quality, efficacy, and integrity of the PV system as well as the compliance to the legal requirements.*
- *Qualifications, nomination and responsibilities of the QPPV/LSR are defined in Module I.*

Throughout all Modules of the LGVP, there is a consistent reference to MAHs as the responsible entities for conducting all pharmacovigilance activities and adhering to the specified requirements. However, as depicted in figure 1, when the MAH is represented by a service provider (such as a local agent or subcontracted organization), it is implicit that the procedures and obligations outlined in this guideline are to be entrusted to the representing entity, while still being under the supervision and oversight of the MAH.

The below diagram (Figure 2) summarizes the submission requirements for the PSMF and/or PSSF with a specific distinction between two categories of MAH/Applicants: National and Multinational.

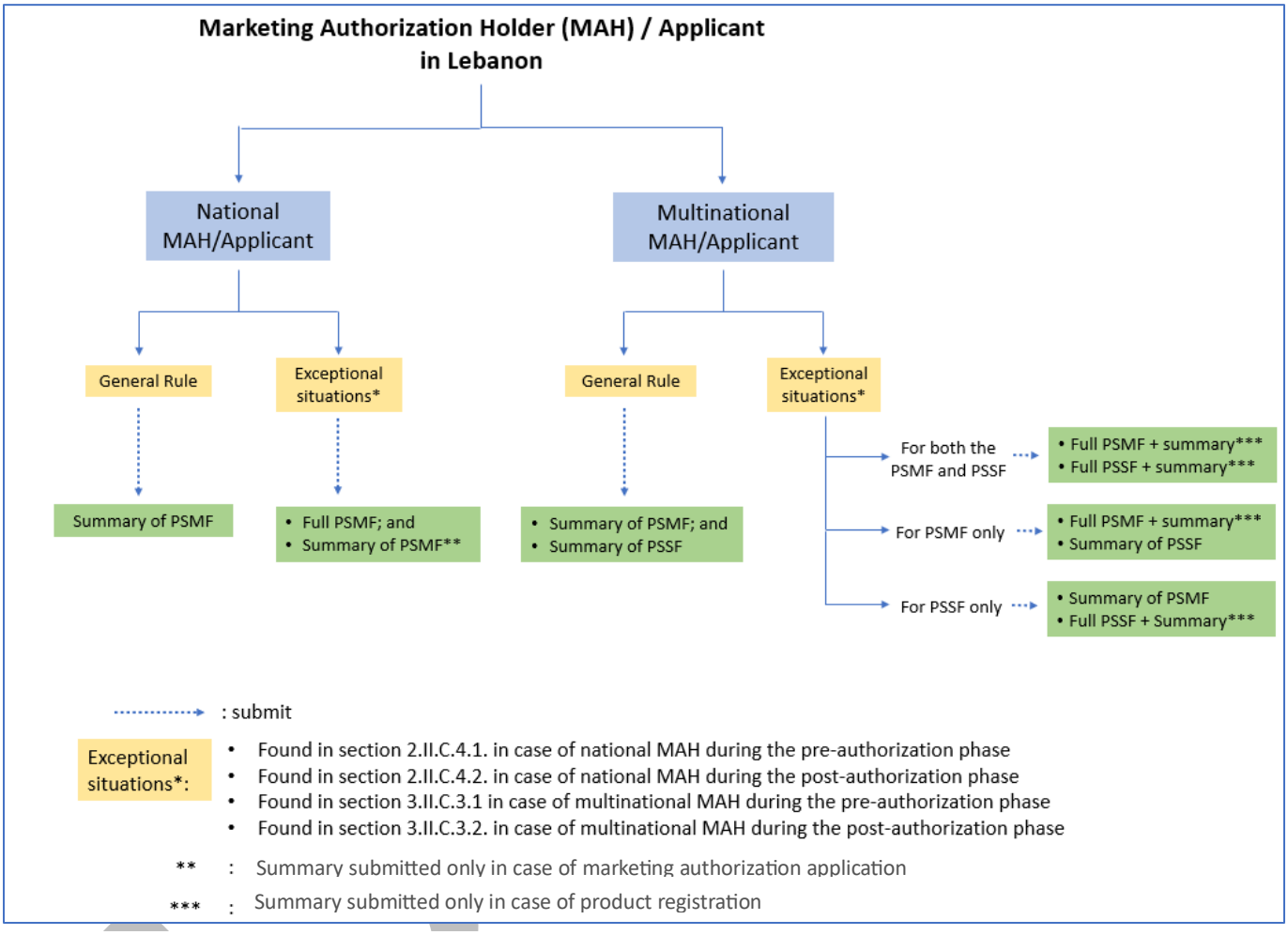

Figure 2: PSMF and PSSF submission requirements

Legend:

- *For national MAHs, only a summary of the PSMF is to be submitted except in certain situations where the full PSMF should be submitted. These exceptional situations are defined in section 2.II.C.4.1. for the pre-authorization phase, and 2.II.C.4.2. for the post-authorization phase.*
- *For multinational MAHs, only a summary of the PSMF and a summary of the PSSF are to be submitted except in situations defined in section 3.II.C.3.1. for the pre-authorization phase, and 3.II.C.3.2. for the post-authorization phase.*
  - *If these exceptions apply to both the PSMF and the PSSF, the full PSMF and PSSF along with their summaries are to be submitted;*
  - *If these exceptions apply to the PSMF only, the full PSMF along with its summary are to be submitted, while only a summary of the PSSF is to be submitted;*
  - *If these exceptions apply to the PSSF only, the full PSSF along with its summary are to be submitted, while only a summary of the PSMF is to be submitted.*
- *The same submission requirements apply during the pre- and post-authorization phases, but with different exceptional situations, each defined in their respective sections.*

Part 2: Pharmacovigilance System Master File (PSMF) requirements for national MAHs/ applicants in Lebanon

This part delivers details on the requirements of the PSMF for national MAHs/applicants, and their representatives (local agent/subcontracted organization) in Lebanon.

2.II.A. Introduction

The PSMF is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more medicinal products authorized for use in Lebanon.

The PSMF should be located either where the main pharmacovigilance activities of the MAH are performed or at the site where the Qualified Person responsible for Pharmacovigilance (QPPV) operates.

A pharmacovigilance system summary information is to be included in the marketing authorization application and submitted to the national competent authority in Lebanon. This summary includes information on the location of the PSMF (see section 2.II.B.2.1.).

This part of the Module provides detailed guidance regarding the requirements for the PSMF, including its maintenance, content, and associated submissions to the national competent authority in Lebanon.

2.II.B. Structures and processes

In accordance to the present GVP guideline, the establishment of a PSMF is mandatory, and the national competent authority in Lebanon will further introduce regulations to address any ambiguities regarding its implementation.

The content and management of the PSMF applies irrespective of the organizational structure of a MAH, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the QPPV's residence is the location at which he/she carries out his/her tasks.

The content of the PSMF should reflect the availability of safety information for all medicinal products covered by the system, presenting information on the pharmacovigilance system not just confined to local or regional activities.

2.II.B.1. Objectives

The PSMF should describe and demonstrate compliance with pharmacovigilance requirements, while also supporting the responsibilities and supervisory duties of the QPPV, facilitating audits, inspections, and assessment by the national competent authority during marketing authorization application(s) or post-authorization processes.

By producing and maintaining the PSMF, the MAH and the QPPV can ensure system compliance, identify deficiencies or non-compliance, and become aware of potential risks or failures in specific aspects of pharmacovigilance. This information helps in effectively producing, managing and enhancing the pharmacovigilance system. Moreover, submitting a summary of the MAH's pharmacovigilance system, provision of the content of the PSMF, and its change history allows for smooth conduct of national competent authority inspections using a risk assessment approach.

Responsibilities of MAHs and applicants towards the PSMF are described in detail in section 2.II.C.

2.II.B.2. Registration and maintenance

2.II.B.2.1. Location

The PSMF should be located either at the site where the main pharmacovigilance activities are performed or at the site where the QPPV operates, irrespective of the format (paper-based or electronic format file). Based on this rule and on the definition of the scope of MAHs/applicants introduced in Part 1 of this Module, the PSMF of Lebanese national MAHs/Applicants should be located in Lebanon since their main pharmacovigilance activities are performed in Lebanon, their PSMF should accordingly be located in Lebanon.

Details about the location of the PSMF are required to be notified to the national competent authority, and any change to the location should be notified immediately in order to have the information updated.

The location information needed includes a physical office address or a contracted third party. If the PSMF is electronic, the location must be where the data stored can be directly accessed and this is sufficient in terms of a practical electronic location. The main site of pharmacovigilance activity should be determined by considering the most relevant site for the whole system. The MAH should have an appropriate rationale for the location decision. If a main site cannot be determined, then the location should default to the site where the QPPV operates.

2.II.B.2.2. Registration

All PSMFs must be registered at the level of the national competent authority in Lebanon. The MAH should submit for such registration and should notify the national competent authority to update the database with the location of the PSMF for each product, and update the information immediately upon change.

2.II.B.2.3. Transfers of responsibilities for the PSMF

The pharmacovigilance system may evolve over time, and changes to responsibilities and activities related to the PSMF must be recorded and managed properly (see sections 2.II.B.4.2. and 2.II.B.4.8.) to ensure that the MAHs fulfill their obligations. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the PSMF should also be notified to the QPPV in order to support their authority to make improvements to the system. These changes or modifications related to the submitted PSMF should be shared with the national competent authority. The types of changes that should be routinely and promptly notified to the QPPV are:

- Updates to the PSMF or its location that are notified to the national competent authority;
- The addition of corrective and/or preventative actions to the PSMF (e.g. following audits and inspections);
- Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
- Changes in arrangements for the provision of the PSMF to the national competent authority;
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of Periodic Safety Update Report (PSUR) production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;

- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activities e.g. new indications, studies, or others.

The QPPV 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/her responsibility (see GVP Module I).

2.II.B.3. Representation of pharmacovigilance systems

The PSMF should describe the pharmacovigilance system for one or more of the MAH's medicinal products. If the MAH deals with various categories of medicinal products, separate pharmacovigilance systems may be applicable, and each of these systems must be described in a distinct PSMF. These files will collectively cover all medicinal products held by the MAH.

- A single QPPV should be appointed to be responsible for the establishment and maintenance of one pharmacovigilance system described in a PSMF.
- If multiple MAHs share a pharmacovigilance system, each MAH is responsible for having its own PSMF that adequately describes the pharmacovigilance system applicable to its products.
- A single QPPV may fulfil the role of QPPV for more than one pharmacovigilance systems within the same MAH.
- A single QPPV may be employed by more than one MAH (i.e. only in case of subcontracting to a third-party organization) for a shared or for separate pharmacovigilance systems.
- The ability of a QPPV to adequately oversee more than one pharmacovigilance system depends on several factors including but not restricted to the number of medicinal products covered by that system, the safety profile of these products and the complexity of the MAH organizational structure. Depending on these factors, it is NOT expected that a QPPV can adequately fulfil all these obligations for more than 5 MAHs in maximum.
- When delegating any activities concerning the pharmacovigilance system and its master file, the MAH retains ultimate responsibility for the pharmacovigilance system, for ensuring submission of information about the PSMF location, maintenance and its provision to the national competent 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.

- Where applicable, a list of all PSMFs held by the same MAH should be provided in the annex (see section 2.II.B.4.8.); this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).

2.II.B.4. Information to be included in the pharmacovigilance system master file

The PSMF should include documents to describe the pharmacovigilance system. These documents are described in the following subsections.

The content of the PSMF should reflect the availability of safety information for medicinal products authorized in Lebanon. The content should be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex headings described in section 2.II.B.6.1. The main principle for the structure of the content of the PSMF is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system.

Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the shared updates as well as the PSMF annexes. The control associated with change of content is described in section 2.II.B.5.

It is accepted that, where no marketing authorization (and master file) previously existed in Lebanon, there may be information that cannot be initially provided, for example, compliance information, however, descriptions of what will be implemented should be provided instead.

2.II.B.4.1. PSMF section on the qualified person for pharmacovigilance

For the QPPV, contact details should be provided in the marketing authorization application.

The information relating to the QPPV provided in the PSMF should include:

- A description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;

- Summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance;
- Details of back-up arrangements to apply in the absence of the QPPV;
- Checklist on the following required practical experience/trainings (Table 1). Taking into consideration that pharmacovigilance practice and regulations are relatively new in Lebanon, thus having an experienced QPPV may be challenging. Accordingly, it is accepted by the national competent authority that the QPPV qualifications may be expressed in terms of his/her PV training rather than his/her practical experience in pharmacovigilance. Under these circumstances, once the QPPV is appointed, the MAH is responsible of providing the unachieved trainings in light of the checklist in Table 1 below. To note that this provision is applicable only during a transitional period, and the national competent authority will determine the specific duration and conditions of this transitional period.

A list of tasks that have been delegated by the QPPV should also be included in the Annexes (see section 2.II.B.4.8.).

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance. The contact details supplied should include name, postal, telephone and e-mail and represent the usual working address of the QPPV, which may therefore be different to a MAH address. If the QPPV is employed by a third party, even if the usual working address is an office of the MAH, this should be indicated and the name of the company the QPPV works for provided.

Table 1: Checklist on the required practical experience/ trainings for QPPVs
(Adapted from the Guideline on Good Pharmacovigilance Practices (GVP) for Arab Countries)

Topic	**Practical experience** * (insert √ or X in the respective field)
▪ Pharmacovigilance methods	
▪ MedDRA coding.	
▪ ICSRs processing activities	
▪ Evidence based –medicine, How to conduct literature search.	
▪ Causality assessment	
▪ Case Narrative Writing for Reporting Adverse Events	
▪ Pharmacovigilance quality management	
▪ Pharmaco-epidemiology	
▪ Biostatiscis	
▪ Signal detection	
▪ Medical Aspects of Adverse Drug Reactions	
▪ Risk benefit assessment in Pharmacovigilance	
▪ National pharmacovigilance regulations	
▪ How to prepare PSUR & Addendum of clinical overview	
▪ Pharmacovigilance Planning and Risk Management Plans	
▪ How to prepare PSMF	
▪ Risk communication, DHPC	

*During the transitional period: add 3rd column to highlight the trainings; the table header will be as follow (insert √ or X in the respective field):

Topic	Practical experience	Training
▪		
▪		

2.II.B.4.2. PSMF section on the organizational structure of the marketing authorization holder

A description of the organizational structure of the MAH relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments, the QPPV position in the organization, and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations.

Specifically, the PSMF should describe the following:

- Organizational structure of the MAHs, indicating the position of the QPPV in the organization;
- Site(s) where pharmacovigilance functions are performed, encompassing various activities such as Individual Case Safety Reports (ICSRs) collection, evaluation, safety database case entry, PSUR production, signal detection and analysis, risk management plan management, pre- and post-authorization study management, and management of safety variations;
- Description of delegated activities and services subcontracted by the MAH to fulfill pharmacovigilance obligations, including arrangements with other parties in the country or abroad. Links with other organizations, such as co-marketing agreements and contracts related to pharmacovigilance activities, should be outlined, specifying the involved parties, roles, and concerned products and territories. The list should be organized according to:
    - Service providers: medical information, auditors, patient support program providers, study data management, etc.;
    - Commercial arrangements: distributors, licensing partners, co-marketing, etc.;
    - Other technical providers: hosting of computer systems, etc..

  Individual contractual agreements must be accessible to the national competent authority upon request, as well as during inspection and audit processes, with details specified in Annexes (see section 2.II.B.4.8.).

2.II.B.4.3. PSMF section on the sources of safety data

2.II.B.4.3.1. Parties responsible for safety data collection

The description of the main units for safety data collection should include all parties responsible for solicited and spontaneous case collection for products authorized in Lebanon. Information about third parties (license partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements.

Description supported by flow diagrams should be used to indicate the main stages, timeframes and parties involved. The description of the process for ICSRs from collection to reporting to the national competent authority should indicate the departments and/or third parties involved.

2.II.B.4.3.2. Sources of safety data

For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programs sponsored by the MAH through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversights. It is recommended that the list should be comprehensive for products authorized in Lebanon, irrespective of indication, product presentation or route of administration. The list should describe, on a national basis, the status of each study/program, 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/programs and should include ongoing studies/programs as well as studies/programs completed in the **last two years** and may be located in an Annex or provided separately.

2.II.B.4.4. PSMF section on computerized systems and databases

The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information should be described in the PSMF.

Where multiple computerized systems/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 computerization within the pharmacovigilance system can be understood.

2.II.B.4.5. PSMF section on pharmacovigilance processes

Clear written procedures represent an essential element of any pharmacovigilance system.

A description of the procedural documentation available (Standard Operating Procedures (SOPs), manuals, at a global and/or national level etc.), the nature of the data held (e.g. the type of case data

retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the PSMF.

A description of the process, data handling and records for the performance of pharmacovigilance covering the following aspects should 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;
- PSUR scheduling, production and submission;
- Communication of safety concerns to consumers, healthcare professionals and the national competent authority;
- Implementation of safety variations to the Summary of Product Characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications of safety variations to the 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. The description must be accompanied by the list of the following processes for compliance management, as well as interfaces with other functions:

1. The continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and appropriate measures are taken by the MAH;
2. The scientific evaluation by the MAH of all information on the risks of medicinal products;
3. The submission of accurate and verifiable data on serious and non-serious adverse reactions to the national competent authority in Lebanon within the time limits provided in the national regulations;
4. The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;

5. Effective communication by the MAH with the national competent authority, including communication on new risks or changed risks, the PSMF, risk management systems, risk minimization measures, periodic safety update reports, corrective and preventive actions, and post-authorization studies;
6. The update of product information by the MAH in the light of scientific knowledge, and on the basis of a continuous monitoring by the MAH of information released by the national competent authority;
7. Appropriate communication by the MAH of relevant safety information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to the national competent 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 Annexes, should comprise in cross matching with each one of the topics highlighted above in this section the topic name, 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.

2.II.B.4.6. 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 monitoring methods applied and should contain as a minimum:

- An explanation of how the reporting of ICSRs is assessed. In the annex of the PSMF, 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 the national competent authority regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timeliness of PSUR reporting to the national competent authority (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 national competent authority 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 Key Performance Indicators (KPIs) should be provided in the Annex to the PSMF, alongside the results of (actual) performance measurements.

Any deviation or non-compliance which is detected either by the MAH or by the national competent authority should be mentioned and justified, and the appropriate corrective and preventive actions should be taken and described in the PSMF.

2.II.B.4.7. 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 should include:

Document and record control

Provide a description of the archiving arrangements for electronic and/or hard copy versions of the different types records and documents for pharmacovigilance and quality system (see also Module I).

Procedural documents

• A general description of the types of documents used in pharmacovigilance (SOPs, 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.

• A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed should be provided, and the detailed guidance for the inclusion of these is in section 2.II.B.4.5.

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.

Training should be done in accordance to a training plan, and this training plan should be provided on the related section within the PSMF.

• A 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, which may be provided in the section describing the organizational structure (see section 2.II.B.4.2)

• Information about sites where the personnel are located (this is described under sections 2.II.B.4.2 and 2.II.B.4.3) whereby the sites are provided in the PSMF in relation to the organization of specific pharmacovigilance activities and in the Annexes, which provide the list of site contacts for sources of safety data. However, a description should be provided in order to explain the training organization in relation to the personnel and site information;

• A summary description of the training concept, including a reference to the location training files, record as well as the trainings materials.

Auditing

Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. A description of the risk-based 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 in section 2.II.B.4.8. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of 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 should also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the national criteria for major or critical findings should be indicated (see GVP Module IV).

The audit report must be documented within the quality system; in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the 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). In case corrective and preventative action plans 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 should 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.

2.II.B.4.8. Annex to the PSMF

An annex to the PSMF should contain the following documents:

- A list of medicinal products covered by the PSMF including the name of the medicinal product, the name of the active substance(s), and the country(ies) in which the authorization is valid;

  The list of medicinal products authorized in Lebanon should also include the national registration number, its marketing status and export countries where the product is authorized or on the market.

  The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exists (for example risk minimization measures contained in the risk management plan or laid down as conditions of the marketing authorization, non-standard PSUR periodicity).

- The monitoring information may be provided as a secondary list. For marketing authorizations that are included in a different pharmacovigilance system; or if third-party agreements exist to delegate

the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs. Where pharmacovigilance systems are shared, all products that utilize the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organized per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the compliance management (see section 2.II.B.4.5.);
- A list of contractual agreements covering delegated activities including the pharmaceutical products concerned;
- A list of tasks that have been delegated by the QPPV;
- A list of all completed audits, for a period of five years, and a list of audit schedules;
- Where applicable, a list of performance indicators (see section 2.II.B.4.6.);
- Where applicable, a list of other PSMFs held by the same MAH. This list should include PSMF number(s), and the name of MAH of the QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not a MAH, the name of the service provider should also be included;
- A logbook of any change of the content of PSMF file made within the last five years except the changes in annexes and the following QPPV information: CV, contact details, back-up arrangements and contact person for pharmacovigilance on the national level. In addition, other change control documentation should be included as appropriate. Documented changes should include at least the date, person responsible for the change and the nature of the change.

The positioning of content in the Annex is further outlined; the bulleted points are descriptions of possible content (and not required headings):

- <u>Annex A: The QPPV for the national pharmacovigilance system:</u>

All documents for qualification and experience evidences. (Required for all PV staff);

  - 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.

- <u>Annex B: The organizational structure of the MAH:</u>
  - The lists of contracts and agreements;

- Official organogram;
- A copy of the individual contractual agreements.

- Annex C: Sources of safety data:
  - Lists associated with the description of sources of safety data e.g. affiliates and third-party contacts.
- Annex D: Computerized systems and databases
- Annex E: Pharmacovigilance process, and written procedures:
  - Lists of procedural documents.
- Annex F: Pharmacovigilance system performance:
  - Lists of performance indicators;
  - Current results of performance assessment in relation to the indicators.
- Annex G: Quality system:
  - Audit schedules;
  - List of audits conducted and completed.
- Annex H: Products:
  - List(s) of products covered by the PSMF;
  - Any notes concerning the MAH per product.
- Annex I: Document and record control:
  - 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.

Documentation to support notifications and signatures concerning the PSMF are required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E **should NOT** be renamed to Annex D in circumstances where no Annex concerning computerized systems and databases is used, Annex D should simply be described as "unused" in the indexing, in order that recipients of the PSMF are assured that missing content is intended.

The competent authority in Lebanon may request any other additional documents which related to any PV activities or functions, and the MAH should provide them in the related Annex as per the authority's request.

2.II.B.5. Change control, logbook, versions and archiving

It is necessary for MAHs to implement change control systems and to have robust processes in place to continuously be informed of relevant changes in order to maintain the PSMF accordingly. The national competent authority may solicit information about important changes to the pharmacovigilance system, such as, but not limited to:

- Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
- Organizational changes, such as takeovers, mergers, the sites at which pharmacovigilance is conducted or the delegation/transfer of PSMF management.
- In addition to these changes being documented in the PSMF for the purpose of change control (in the logbook), the QPPV should always been kept informed of these changes.

Changes to the PSMF should be recorded, such that a history of changes is available (specifying the date and the nature of the change), descriptive changes to the PSMF must be recorded in a logbook.

Change history for the information contained in the Annexes may be “on demand”, in which case the logbook would indicate the date of the revision of PSMF content and/or Annex update(s), the history of changes for Annex content would also be updated.

MAHs should be able to justify their approach and have document control procedures in place to govern the maintenance of the PSMF. As a basis for audit and inspections, the PSMF provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

Changes to the PSMF should also account for shared pharmacovigilance systems and delegated activities. A record of the date and nature of notifications of the changes made available to the national competent authority, the QPPV and relevant third parties should be kept in order to ensure that change control is fully implemented.

The PSMF should be retained in a manner that ensures its legibility and accessibility.

2.II.B.6. Pharmacovigilance system master file presentation

The PSMF should be continuously accessible to the QPPV and to the national competent authority on request. The information should be succinct, accurate and reflect the current system in place, which means that whatever format is used, 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.

Although provision of the document within 14 days of request by the national competent authority is required, MAHs should be aware that immediate access to the PSMF may also be required by the national competent authority, at the stated PSMF location or QPPV site (if different).

2.II.B.6.1. Format and layout

The PSMF may be in electronic form and printed copy can be provided to the national competent authority upon request. Regardless of format, the master file should be legible, comprehensive, easily accessible, and should 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. The PSMF should be written in English (unless otherwise is requested by the national competent authority), indexed in a manner consistent with the headings described in this Module, and should allow easy navigation in the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index. The documents and particulars of PSMF should be presented with the following headings and, in the case of a hard copy, in the order outlined:

<u>Cover page to include:</u>

- The unique number assigned by the national competent authority to the PSMF (if applicable);
- 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.

The headings used in section 2.II.B.4. “Information to be included in the PSMF” should be used for the main content of the PSMF. The minimum required content of the Annexes is outlined in section 2.II.B.4.8 “Annex to the PSMF”, and additional information may be included in the Annexes, provided that the requirements for the content of the main sections (2.II.B.4.1-7) are also met.

2.II.C. Operations for PSMF in Lebanon

2.II.C.1. Responsibilities

2.II.C.1.1. Marketing authorization holders and applicants

MAHs should have a pharmacovigilance system in place to ensure the monitoring and supervision of one or more pharmaceutical products. They are also responsible for introducing and maintaining a PSMF that records the pharmacovigilance system in place with regard to one or more authorized products. A single QPPV should be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

When submitting an initial application for marketing authorization, applicants must include a summary of their pharmacovigilance system, which details the system that will be operational and in effect at the time the marketing authorization is granted and the product is introduced to the market. During the evaluation of a marketing authorization application, the applicant may be requested to provide a copy of the PSMF for review. The MAH/applicant is responsible for establishing the PSMF (at any MAH or contractual partner site including the site of a contractor or marketing partner), and to submit for registering its PSMF location with the national competent authority. The PSMF should describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in the future may be included, but these should be clearly described as planned rather than established or current.

The PSMF creation, maintenance in a current and accessible state (permanently available for audit and inspection purposes) and provision to the national competent authority can be outsourced to a third party, but the MAH retains ultimate responsibility for compliance with the legal requirements.

When the QPPV and related contact details change or when the location of the PSMF changes, the MAH is required to notify/submit the appropriate variation application(s) to the national competent authority as applicable.

2.II.C.2. Accessibility to the pharmacovigilance system master file

The PSMF should be maintained in a current state and be permanently available to the QPPV. It should also be permanently available for inspection, at the site where it is kept (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced.

The MAH should maintain and make available on request a copy of PSMF. The MAH must submit the copy within 14 days after receipt of the request from the national competent authority in Lebanon (unless otherwise stated in the request). The PSMF should be submitted in a readable electronic format or clearly arranged printed copy.

When the MAH/applicant has not previously submitted the PSMF in Lebanon or is in the process of establishing a new pharmacovigilance system; the first PSMF submission should be accompanied by the complete version of pharmacovigilance SOPs.

In the situation where the same PSMF is used by more than one MAH (where a common pharmacovigilance system is used), the concerned PSMF should be accessible to each, as any of the applicable MAHs should be able to provide the file to the national competent authority within 14 days, upon request (unless otherwise stated in the request).

2.II.C.3. Summary of the applicant's pharmacovigilance system

Except in the situations described in section 2.II.C.4. where the full PSMF (along together with its summary) is requested to be submitted in the marketing authorization application; only a **summary of the applicant's PSMF** is required to be included in the marketing authorization application, encompassing the following elements:

- Proof that the applicant has at their disposal a QPPV residing in Lebanon;
- The contact details of the qualified person;
- Statement signed by the applicant to the effect that they have the necessary means to fulfil the pharmacovigilance tasks and responsibilities listed in the present GVP Modules;
- A reference to the location where the PSMF for the pharmaceutical product is kept.

2.II.C.4. Submission requirements for the pharmacovigilance system master file

Figure 2 presented in Part 1 of this Module summarizes the PSMF submission requirements for national MAHs.

2.II.C.4.1. Pre-authorization

During the assessment of new marketing authorization applications (i.e. in the pre-authorization phase), the full PSMF is not routinely requested. Instead, the "summary of the PSMF" should be submitted (Figure 2).

Exceptionally to this rule, the national competent authority may request submission of the full PSMF along together with its summary 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 (Figure 2):

- If the applicant has not previously held a marketing authorization in Lebanon, full PSMF is appropriate to review the description of a pharmacovigilance system;
- If the applicant has not previously submitted the PSMF or is in the process of establishing a new pharmacovigilance system;
- If the applicant had major changes in its organization, such as mergers and acquisitions or in its pharmacovigilance system;
- If the applicant has major or critical findings in the previous pharmacovigilance system assessment by the national competent authority;
- If the applicant has a history or culture of pharmacovigilance non-compliance; previous information (e.g. inspection history and non-compliance notifications or information from other authorities). In addition to the submission of the full PSMF, if the MAH 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 (see Module III);

- Where specific concerns about the pharmacovigilance system and/or the product safety profile exist;
- Any other situation as seen appropriate by the national competent authority.

2.II.C.4.2. Post-authorization

The full PSMF (including annexes) may be requested on an ad-hoc basis in the following situations (Figure 2):

- If a new pharmacovigilance system is being implemented;
- If product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified;
- In preparation for a pharmacovigilance inspection;
- Any other situation as seen appropriate by the national competent authority.

Part 3: National Pharmacovigilance Sub-System File (PSSF) and Global PSMF requirements for multinational MAHs/applicants in Lebanon

This part delivers details on the requirements and submission of the national PSSF of multinational MAHs/applicants in Lebanon and their representatives (local agent/subcontracted organization) in Lebanon.

3.II.A. Introduction

All MAHs must have an appropriate system of pharmacovigilance in place. It is understood that for multinational MAHs/applicants; the pharmacovigilance activities in Lebanon function as a part or **sub-system of its global pharmacovigilance system and integrate with it.** Accordingly, the national competent authority adapted the requirements provided in this part from the Arab Guidelines on Good Pharmacovigilance Practice (Arab GVP).

3.II.B. Structures and processes

The content of the PSMF should reflect global availability of safety information for medicinal products authorized for the MAH, with information on the pharmacovigilance system to the local or regional activities.

Despite this fact, pharmacovigilance activities on the national level as described in the PSMF may not be applied to the same extent by all the MAH's national (scientific) offices/affiliates. Furthermore, some additional national requirements and details may also apply. Accordingly, multinational MAHs/applicants should provide a clear illustration of the key elements **of both the global pharmacovigilance system** and the **national pharmacovigilance sub-system**, highlighting the role of the LSR, which pharmacovigilance activities are carried out in Lebanon, which are carried out in the headquarters/globally and how they integrate together.

3.II.B.1. Objectives

For multinational MAHs/Applicants, the National Pharmacovigilance Sub-System File (PSSF) describes the key elements of pharmacovigilance activities in Lebanon. The content of the PSMF is accepted to be according to European Good Pharmacovigilance Practice which is the basis of the present guideline. In regards to multinational MAHs/Applicants, all the regulations described in Part 2 of this Module apply to the PSMF.

For multinational MAHs/Applicants, the following two types of documents are required for submission:

1. The PSMF prepared according to the guidelines in Part 2 of this Module.
   A global PSMF (including its annexes) prepared in accordance with the EMA GVP or the Arab GVP is acceptable; and

2. The National PSSF describing the key elements of pharmacovigilance activities in Lebanon, developed in the present Part 3.

Submission requirements of each document are detailed in section 3.II.C.

3.II.B.2. Registration and maintenance

3.II.B.2.1. Location, registration and transfer of responsibilities

A Multinational MAH/Applicant operates on a global/regional scale. Since their main pharmacovigilance activities take place outside of Lebanon, their PSMF can accordingly be located in the country of headquarters or where the main pharmacovigilance activities take place, provided that:

- The Global PSMF (including annexes) is made available to the national competent authority in Lebanon at any time; and
- The local affiliate or scientific office (if applicable) of the MAH/applicant has a detailed description on the pharmacovigilance system/activities on the local level (PSSF).

Only for the PSSF, details about its location are required to be notified to the national competent authority, and any change to the location should be notified immediately in order to have the information updated.

On the other hand, location of the global PSMF will be reported in the PSMF itself and summary when submitted.

The registration and continuous maintenance described in section 2.II.B.2.2 apply only to the PSSF.

The transfer of responsibilities described in section 2.II.B.2.3 applies to the PSSF. It is expected that the same practice is already in place for the global PSMF.

3.II.B.3. Representation of pharmacovigilance systems

The representation described in section 2.II.B.3. applies to the PSSF of multinational MAHs, with the LSR adhering to the same rules as those applicable to the QPPV. Duties/role of the LSR are described in Module I of this guideline.

3.II.B.4. Information to be included in the national PSSF

The PSSF should include information and documents to describe the pharmacovigilance sub-system at the national level in Lebanon. The content of the national PSSF should be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex headings described in section 3.II.B.6.1. The national PSSF should be maintained in a current state and be permanently available to the LSR.

On the other hand, the PSMF prepared according to the EMA GVP or Arab GVP which are the basis of this guideline and developed in Part 2 of this Module is acceptable.

3.II.B.4.1. National PSSF section on the Local Safety Responsible (LSR)

For the LSR, contact details should be provided in the marketing authorization application. The information relating to the LSR provided in the national PSSF should include:

- A description of the LSR responsibilities guaranteeing that the LSR has sufficient authority over the pharmacovigilance activity on the national level in order to promote, maintain and improve compliance with national regulations;
- A summary curriculum vitae with the key information on the role of the LSR;
- Details of back-up arrangements to apply in the absence of the LSR;
- Checklist on the required practical experience/ trainings (Table 2). Taking into consideration that pharmacovigilance practice and regulations are relatively new in Lebanon, thus having an

experienced LSR may be challenging. Accordingly, it is accepted by the national competent authority in Lebanon that for only a transitional period the LSR qualifications may be expressed in terms of his pharmacovigilance training rather than his practical experience in pharmacovigilance. Under these circumstances, once the LSR is appointed, the MAH is responsible of providing the unachieved trainings in light of the checklist in Table 2. To note that this provision is applicable only during a transitional period, and the national competent authority will determine the specific duration and conditions of this transitional period.

If applicable, a list of tasks that have been delegated by the LSR should also be included in the Annexes (see section 3.II.B.4.8.). This should outline the activities that are delegated and to whom. The details provided in relation to the LSR should also include the description of the LSR qualifications, experience and registrations relevant to pharmacovigilance. The contact details supplied should include name, postal, telephone and e-mail and represent the usual working address of the LSR.

Table 2: Checklist on the required practical experience/trainings for LSRs

Topic	**Practical experience*** (insert √ or X in the respective field)
▪ Pharmacovigilance methods	
▪ MedDRA coding.	
▪ ICSRs processing activities	
▪ Evidence based –medicine, How to conduct literature search.	
▪ Causality assessment	
▪ Case Narrative Writing for Reporting Adverse Events	
▪ Pharmacovigilance quality management	
▪ Introduction to pharmaco-epidemiology	
▪ Biostatiscis	
▪ Basics of signal detection	
▪ Medical Aspects of Adverse Drug Reactions	
▪ Risk benefit assessment in Pharmacovigilance	
▪ National pharmacovigilance regulations	
▪ PSUR overview & national appendix	
▪ RMP overview & National display	
▪ PSMF overview & national PSSF	
▪ Risk communication, DHPC	

*During the transitional period: add 3rd column to highlight the trainings; the table header will be as follow (insert √ or X in the respective field):

Topic	Practical experience	Training
▪		
▪		

3.II.B.4.2. National PSSF section on the organizational structure of the MAH's local office

- A description of the organizational structure of the MAH's local/scientific office relevant to the national pharmacovigilance sub-system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance department and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the national PSSF should describe:
  - The organizational structure of the MAH's local/scientific office, showing the position of the LSR in the organization;
  - The site(s) where the pharmacovigilance functions on the national level are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production (integration with global system), signal detection and analysis (integration with global system), risk management plan management, pre- and post-authorization study management, and management of safety. Diagrams may be particularly useful; the name of the department or third party should be indicated.

- Delegated activities: When no local/scientific office exists for a MAH in Lebanon, or when no pharmacovigilance department exists at the level of the scientific office, a delegation is needed. The national PSSF, where applicable, should contain a description of the delegated activities and/or services relating to the fulfillment of pharmacovigilance obligations.
- Links with other organizations, such as co-marketing agreements and contracting of pharmacovigilance activities on the national level should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories. The list should be organized according to:
  - Service providers: medical information, auditors, patient support program providers, study data management, etc.;
  - Commercial arrangements: distributors, licensing partners, co-marketing, etc.;
  - Other technical providers: hosting of computer systems, etc..

  Individual contractual agreements should be annexed with the national PSSF when the latter is submitted. Individual contractual agreements should be made available at the request of the national competent authority at any time or during inspection and audit and the list provided in the Annexes (see section 3.II.B.4.8).

3.II.B.4.3. National PSSF section on the sources of safety data

3.II.B.4.3.1. Parties responsible for safety data collection

The description supported by flow diagrams should be used to indicate the main stages of safety data collection for solicited and spontaneous case collection for products authorized in Lebanon, timeframes and parties involved. However represented, the description of the process for ICSRs from collection to reporting to the national competent authority should indicate the departments and/or third parties involved.

3.II.B.4.3.2. Sources of safety data

For the purposes of inspection and audit of the pharmacovigilance system, safety data sources include data arising from study sources, including any studies, registries, surveillance or support programs sponsored by the marketing authorization holder through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and headquarters QPPV and LSR oversights. It is recommended that the list should be comprehensive for products authorized in Lebanon (i.e. on the national level), irrespective of indication, product presentation or route of administration. The list should describe, on the national basis, the status of each study/programme, 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 or provided separately.

3.II.B.4.4. National PSSF section on computerized systems and databases

It is understood that for multinational MAH, the global safety database might be located outside Lebanon (at the site where the main pharmacovigilance activities are performed globally e.g. Headquarters). However, the LSR must have online access to national safety cases and all national pharmacovigilance data of Lebanon; otherwise at least backup database of this national data should always be kept in the local office. The location, functionality and operational responsibility for computerized systems and databases used (on the national level) to receive, collate, record and report

safety information and an assessment of their fitness for purpose should be described in the national PSSF. Where multiple computerized systems/databases are used on national level, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerization within the pharmacovigilance system can be understood. The validation status of key aspects of computer system functionality should also be described; 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 non-electronic 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.

3.II.B.4.5. National PSSF section on pharmacovigilance processes

An essential element of any pharmacovigilance system is that there are clear written procedures in place. Module I describes the required minimum set of written procedures for pharmacovigilance. A description of the procedural documentation available on national level (SOPs, manuals, etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the national PSSF. A description of the process, data handling and records for the performance of pharmacovigilance (**on the national level and as appropriate in integration with MAH's headquarters**), covering the following aspects should be included in the national PSSF:

- 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 (in integration with the MAH's headquarters). 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 (in integration with the MAH's headquarters);
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;

- PSUR scheduling, production and submission (see Module VII) (in integration with the MAH's headquarters);
- Communication of safety concerns to consumers, healthcare professionals and the national competent authority;
- Implementation of safety variations to the SmPC and patient information leaflets; procedures should cover both internal (within the MAH) and external communications.
- In each area, the marketing authorization holder should be able to provide evidence of a sub-system that supports appropriate and timely decision making and action on the national level (taking into consideration liaising with the MAH's headquarters).

The description must be accompanied by the **list** of the following **processes for compliance management,** as well as interfaces with other functions (**on the national level and as appropriate in integration with MAH's headquarters):**

1. The continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and appropriate measures are taken by the MAH;
2. The scientific evaluation by the MAH of all information on the risks of medicinal products;
3. The submission of accurate and verifiable data on serious and non-serious adverse reactions to the national competent authority within the time limits provided in the national regulations;
4. The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;
5. Effective communication by the MAH with the national competent authority, including communication on new risks or changed risks, the PSMF and national PSSF, risk management systems, risk minimization measures, periodic safety update reports, corrective and preventive actions, and post-authorization studies;
6. The update of product information by the MAH in the light of scientific knowledge, and on the basis of a continuous monitoring by the marketing authorization holder of information released by the national competent authority;
7. Appropriate communication by the MAH of relevant safety information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and responsibilities of the LSR, responding to the national competent 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 Annexes,

should comprise in cross matching with each one of the topics highlighted above in this section, the topic name, the procedural document reference number, title, effective date and document type (for all SOPs, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified. In addition, any specific local procedures should be also indicated.

3.II.B.4.6. National PSSF section on pharmacovigilance sub-system performance

The national PSSF should contain evidence of the ongoing monitoring of performance of the national pharmacovigilance sub-system including compliance of the main outputs of pharmacovigilance. The national PSSF should include a description of the monitoring methods applied and contain as a minimum (the following should focus on performance on the national level):

- An explanation of how the correct reporting of domestic ICSRs is assessed. In the annex of the PSSF, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting (to the national competent authority) 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 the national competent authority regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timelines of PSUR reporting to the national competent authority in Lebanon concerned (the annex should reflect the latest figures used by the MAH to assess compliance on national level);
- An overview of the methods used to ensure timelines of safety variation submissions compared to internal and the national competent authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to National Display of RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance sub-system should be described and explained. A list of performance indicators must be provided in the Annex to the national PSSF, alongside the results of (actual) performance measurements.

3.II.B.4.7. National PSSF 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 should include:

Document and record control

Provide a description of the archiving arrangements (on national level) for electronic and/or hard copy versions of the different types of records and documents for pharmacovigilance and quality system (see also Module I).

Procedural documents

- A general description of the types of documents used in pharmacovigilance (SOPs, work instructions etc.), the applicability of the various documents at 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. A list of specific procedures and processes related to the pharmacovigilance activities (on the national level) and interfaces with other functions, with details of how the procedures can be accessed must be provided, and the detailed guidance for the inclusion of these is in section 3.II.B.4.5.;

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 such as sales personnel or clinical research staff or others;

- A description of the resource management for the performance of pharmacovigilance activities on the national level: - the organizational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organizational structure (see section 3.II.B.4.2.);
- Information about sites where the personnel are located (see sections 3.II.B.4.2. and 3.II.B.4.3.) whereby the sites are provided in the national PSSF in relation to the organization of specific pharmacovigilance activities. However, a description should be provided in order to explain the training organization in relation to the personnel and site information;

- A summary description of the training concept, including a reference to the location training files, record as well as the trainings materials.

Auditing

- Information about quality assurance auditing of the national pharmacovigilance sub-system should be included in the national PSSF. A description of the approach used to plan audits of the national pharmacovigilance sub-system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the national pharmacovigilance sub-system maintained in the annex referred in section 3.II.B.4.8.

This list should describe the date(s) (of conduct and of report), scope and completion status of audits of 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 national PSSF should also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the criteria for major or critical findings must be indicated (see Module IV).

The audit report must be documented within the quality system; in the PSSF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the 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). In case corrective and preventative action plans have not yet been agreed for a particular audit or finding, the PSSF 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 PSSF, should be identified. The note and associated corrective and preventative action(s), shall be documented in the PSSF 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 national pharmacovigilance sub-system, and providing a basis for audit or inspection, the national PSSF should also describe the process for recording, managing and resolving deviations from the quality system. The national PSSF should also document deviations from pharmacovigilance procedures on the national level, 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.

3.II.B.4.8. Annex to the national PSSF

An annex to the national PSSF should contain the following documents:

- A list of medicinal products covered by this national PSSF in Lebanon. The following should be provided for each medicinal product in the list:

  - The name of the medicinal product;
  - The name of the active substance(s);
  - The marketing authorization number in Lebanon;
  - The presence on the market Lebanon (i.e. marketing status);
  - Other country(ies) in which this product is authorized;
  - The presence on the market in these other country(ies) stated in the list (i.e. marketing status).

The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimization measures contained in the National Display of RMP or laid down as conditions of the marketing authorization, non-standard PSUR periodicity). The monitoring information may be provided as a secondary list. For marketing authorizations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system on the national level or third-party agreements exist to delegate the system, reference to the additional national PSSF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of national PSSF.

Where national pharmacovigilance sub-systems are shared, all products that utilize the national pharmacovigilance sub-system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organized per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered.

- A list of written policies and procedures for the compliance management (see section 3.II.B.4.5.);

- A list of contractual agreements covering delegated activities in Lebanon including the medicinal products concerned. In addition, a copy of the individual contractual agreements should also be included in this annex when the PSMF is submitted to the national competent authority;
- A list of tasks that have been delegated by the LSR (if any);
- A list of all completed audits on the national level, for a period of five years, and a list of audit schedules on the national level;
- Where applicable, a list of performance indicators (see section 3.II.B.4.6.);
- Where applicable, a list of other national PSSF(s) held by the same marketing authorization holder; This list should include the national PSSF number(s), the name of MAH, the name of the LSR responsible for the pharmacovigilance sub-system used. If the pharmacovigilance sub-system is managed by another party that is not a marketing authorization holder, the name of the service provider should also be included.
- A logbook of any change of the content of the national PSSF made within the last five years except the changes in annexes and the following LSR information: CV, contact details, back-up arrangements and contact person for pharmacovigilance on the national level. In addition, other change control documentation should be included as appropriate. Documented changes should include at least the date, person responsible for the change and the nature of the change.

The positioning of content in the Annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):

- Annex A: The LSR for national pharmacovigilance sub-system:
  - The list of tasks that have been delegated by the LSR (if any), or the applicable procedural document;
  - The curriculum vitae of the LSR and associated documents;
  - Contact details.
- Annex B: The organizational structure of the MAH:
  - The lists of contracts and agreements;
  - A copy of the individual contractual agreements relevant to Lebanon.
- Annex C: Sources of safety data
- Annex D: Computerized systems and Databases
- Annex E: Pharmacovigilance Process, and written procedures:
  - Lists of procedural documents

- Annex E: Pharmacovigilance Sub-System Performance:
  - Lists of performance indicators
  - Current results of performance assessment in relation to the indicators
- Annex G: Quality System:
  - Audit schedules (for national pharmacovigilance sub-system);
  - List of audits conducted and completed (for national pharmacovigilance sub-system).
- Annex H: Products:
  - List(s) of products covered by the national pharmacovigilance sub-system described in this national PSSF;
  - Any notes concerning the MAH per product.
- Annex I: Document and Record Control:
  - 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;
  - Documentation to support notifications and signatures concerning the national PSSF, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E should NOT be renamed to Annex D in circumstances where no Annex concerning computerized systems and databases is used, Annex D should simply be described as "unused" in the indexing, in order that recipients of the pharmacovigilance system master file is assured that missing content is intended.

3.II.B.5. Change control, logbook, versions and archiving

The control associated with change of content as described in section 2.II.B.5. apply to the PSSF. It is expected that the same practice is already in place for the global PSMF.

3.II.B.6. National Pharmacovigilance Sub-System File presentation

The national PSSF should be continuously accessible to the LSR and to the national competent authority any time on request. The information should be succinct, accurate and reflect the current system in place, which means that whatever format is used, 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. Although provision of the document **within 14 days of request** by the national competent authority is required, MAHs should be aware that immediate access to the national PSSF may also be required by the national competent authority.

On the other hand, it is expected that the practice described in 2.II.B.6 regarding PSMF presentation, format and layout is already in place for the global PSMF.

3.II.B.6.1. Format and layout

The national PSSF may be in electronic form on condition that a clearly arranged printed copy can be made available to national drugs authorities if requested. In any format, the national PSSF should be legible, complete, 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 it in order to ensure appropriate control over the content and to assign specific responsibilities for the national PSSF in terms of change control and archiving. The national PSSF should be written in English (unless otherwise is requested by the national competent authority in Lebanon), indexed in a manner consistent with the headings described in this Module, and allow easy navigation to the contents with. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index. The documents and particulars of the national PSSF should be presented with the following headings and, if hardcopy, in the order outlined:

<u>Cover Page to include:</u>

- The unique number assigned by the national competent authority to national PSSF (if applicable);
- The name of the MAH, the MAH of the LSR responsible for the national pharmacovigilance sub-system described (if different), as well as the relevant LSR third party company name (if applicable);
- The name of other concerned MAH(s) (sharing the national pharmacovigilance sub-system) (if
- applicable);
- The list of national PSSF(s) for the MAH (concerning products with a different pharmacovigilance sub-system) (if applicable);
- The date of preparation / last update.

The headings used in section 3.II.B.4**.** should be used for the main content of the national PSSF. The minimum required content of the Annexes is outlined in section 3.II.B.4.8., and additional information may be included in the Annexes, provided that the requirements for the content of the main sections (sections 3.II.B.4.1-7) are also met.

3.II.C. Operations for PSSF in Lebanon

3.II.C.1. Accessibility to the pharmacovigilance sub-system file

The MAH should maintain and make available on request a copy of the PSMF and national PSSF. The MAH must submit the copy within 14 days after receipt of the request from the national competent authority in Lebanon (unless otherwise stated in the request). The PSMF and national PSSF should be submitted in a clearly arranged readable electronic format or clearly arranged printed copy.

The same conditions in the table in section 3.II.C.3.1. apply.

3.II.C.2. Summary of the applicant's national pharmacovigilance sub-system

Except in the situations described in section 3.II.C.3. where the full PSSF (along together with its summary) is requested to be submitted in the marketing authorization application; only a **summary of the applicant's national PSSF** and summary of the global PSMF are required to be included in the marketing authorization application.

The content for the PSMF summary described in section 2.II.C.3. apply.

The summary of the applicant's national PSSF should encompass the following elements:

- Proof that the applicant has at their disposal a LSR residing in Lebanon;
- The contact details of the LSR;
- A statement signed by the applicant to the effect that they have the necessary means to fulfil on the national level the pharmacovigilance tasks and responsibilities listed in this GVP modules;
- A reference to the location where the national PSSF for the medicinal product is kept.

3.II.C.3. Submission requirements for multinational MAHs/applicants' PSMF and national PSSF

The PSMF and the national PSSF should be maintained in a current state and should be permanently available to be submitted.

Figure 2 presented in Part 1 of this Module summarizes the PSSF and PSMF submission requirements for multinational MAHs.

3.II.C.3.1. Pre-authorization

During the assessment of new marketing authorization applications (i.e. in the pre-authorization phase), the full PSMF and the full national PSSF (as appropriate) are not routinely requested. Instead, the "summary of the PSMF" and "summary of the national PSSF" (as appropriate) should be submitted (Figure 2).

Exceptionally to this rule, the national competent authority may request submission of the full global PSMF (including annexes) and the PSSF along together with summaries 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 (Figure 2):

- The applicant has not previously held a marketing authorization in Lebanon, full PSMF and the national PSSF are appropriate to review the description of a pharmacovigilance system;
- The applicant has not previously submitted the PSMF and the national PSSF in Lebanon 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;
- The applicant has major or critical findings in the previous assessment of the pharmacovigilance system (global and/or local) by the national drugs authority;
- The applicant has a history or culture of pharmacovigilance non-compliance; previous information (e.g. inspection history and non-compliance notifications or information from other authorities). In

addition to the submission of the full PSMF and national PSSF, if the MAH 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 (see Module III);

- Where specific concerns about the pharmacovigilance system (global and/or local) and/or the product safety profile exist;
- Any other situation as seen appropriate by the national competent authority.

In case that these situations apply to the national PSSF but not the PSMF; then the multinational MAH can submit the "summary of PSMF" and the "national PSSF", and vice versa (Figure 2, Table 3).

The following table summarizes the different scenarios:

Table 3: Conditions for submission of PSFM and PSSF in the pre-authorization phase

Conditions	Document submitted
Situations in 3.II.C.3.1. apply to both PSMF and the National PSSF	• PSMF & summary of PSMF; & • National PSSF & summary of National PSSF
Situations in 3.II.C.3.1. apply to only National PSSF	• Summary of PSMF; & • National PSSF & summary of National PSSF
Situations in 3.II.C.3.1. apply to only PSMF	• PSMF & summary of PSMF; & • Summary of National PSSF
Situations in 3.II.C.3.1. do NOT apply to both the PSMF and the National PSSF	• Summary of PSMF; & • Summary of National PSSF

3.II.C.3.2. Post-authorization

The full PSMF (including annexes) and the full national PSSF (including annexes) may be requested on an ad hoc basis by the national competent authority in the following situations:

- Particularly if a new pharmacovigilance system is being implemented or the MAH has not previously submitted the PSMF and the national PSSF in Lebanon;
- If product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified; or
- In preparation for a pharmacovigilance inspection;
- Any time upon request of the national competent authority.