REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

Lebanese Guideline on Good Pharmacovigilance Practices (LGVP)

Module IV

Pharmacovigilance Audits

Table of Contents

Module IV – Pharmacovigilance audits

IV.A. Introduction

For the purposes of this module, reference to pharmacovigilance audit(s) and pharmacovigilance audit activity(ies) are deemed to include pharmacovigilance system audits and audit(s) of the quality system for pharmacovigilance activities.

The overall description and objectives of pharmacovigilance systems and quality systems for pharmacovigilance activities are referred to in Module I, while the specific pharmacovigilance processes are described in each respective Module of the LGVP.

In this Module, all applicable legal requirements are referenced by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

This Module provides guidance on planning and conducting the legally required audits, the role, context, and management of pharmacovigilance audit activity. This Module is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonization and encourage consistency and simplification of the audit process. The principles in this Module are aligned with internationally accepted auditing standards, issued by relevant international auditing standardization organizations[1] and support a risk-based approach to pharmacovigilance audits.

IV.A.1. Terminology

Audit: A systematic, disciplined, independent**,** and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011 (3.1)[1]**.**

Auditee: [entity] being audited (ISO 19011 (3.7)[1]

Audit finding(s): Results of the evaluation of the collected audit evidence against audit criteria (see ISO19011 (3.4)[2]). Audit evidence is necessary to support the auditors' evaluation results, i.e., the auditor’s

[1] For more details regarding ; the **International Organization for Standardization** (ISO) see www.iso.org ; **Information Systems Audit and Control Association** (ISACA) see www.isaca.org ; **The International Auditing and Assurance Standards Board** (IAASB) see www.ifac.org ; **The International Organization of Supreme Audit Institutions** (INTOSAI) see www.issai.org .

[2] See **International Organization for Standardization** (ISO) see www.iso.org

opinion and report. It is cumulative in nature and is primarily obtained from audit procedures performed during the course of the audit. See also Audit

Auditors' independence: The freedom from conditions that threaten objectivity or the appearance of objectivity. Such threats to objectivity must be managed at the individual auditor, engagement, functional, and organizational levels (IIA International Standards for the Professional Practice of Internal Auditing[3]).

Auditors' objectivity: An unbiased mental attitude that allows internal auditors to perform engagements in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires internal auditors not to subordinate their judgment on audit matters to that of others (IIA International Standards for the Professional Practice of Internal Auditing[3]).

Audit plan: Description of activities and arrangement for an individual audit (see ISO19011 (3.12)[2]). See also Audit

Audit program: Set of one or more audits planned for a specific timeframe and directed towards a specific purpose (see ISO 19011 (3.11)[2]). See also Audit

Audit recommendation: Describes the course of action management might consider to rectify conditions that have gone awry and to mitigate weaknesses in systems of management control (see Sawyer LB et al, 2003)[3]). Audit recommendations should be positive and as specific as possible. They should also identify who is to act on them (Sawyer LB et al, (2003)[4]). See also Audit

Compliance: Conformity and adherence to policies, plans, procedures, laws, regulations, contracts, or other requirements (IIA International Standards for the Professional Practice of Internal Auditing[3]).

Control(s): Any action taken by management and other parties to manage risk and increase the likelihood that established objectives and goals will be achieved. Management plans, organizes, and directs the performance of sufficient actions to provide reasonable assurance that objectives and goals will be achieved (IIA International Standards for the Professional Practice of Internal Auditing[3]).

Evaluation (of audit activities): Professional auditing bodies promote compliance with standards, including quality assurance of their own activities, and codes of conduct, which can be used to address adequate

[3] See **The Institute of Internal Auditors (IIA)**, www.theiia.org

[4] Sawyer LB, Dittenhofer MA. Sawyer's Internal Auditing. 5th ed. Altamonte Springs, FL: The IIA Research Foundation; 2003.

fulfilment of the organization's basic expectations of Internal Audit activity and its conformity to internationally accepted auditing standards.

Head of the organization: see Upper management

Internal Control: Internal control is an integral process that is achieved by an entity's management and personnel and is designed to address risk and provide reasonable assurance that in pursuit of the entity's mission, the following general objectives are being achieved: executing orderly, ethical, economical, efficient and effective operations, fulfilling accountability obligations, complying with applicable laws and regulations and safeguarding resources against loss, misuse and damage (for further information refer to **Committee of Sponsoring Organizations (**COSO) standards[5]).

International Auditing Standards: issued by International Auditing Standardization Organizations.

International Auditing Standardization Organizations: More details regarding: **The Institute of Internal Auditors** (IIA) standards can be found at http://www.theiia.org/guidance/standards-and-guidance/ippf/standards/full-standards; The **International Organization for Standardization** (ISO) standard 19011 —Guidelines for quality and/or environmental management systems auditing. http://www.iso.org/iso/home.html; **Information Systems Audit and Control Association** (ISACA) standards can be found at http://www.isaca.org/Standards;

The International Auditing and Assurance Standards Board (IAASB) standards can be found at http://www.ifac.org/auditing-assurance/clarity-center/clarified-standards;

The International Organization of Supreme Audit Institutions (INTOSAI) can be found at http://www.issai.org/composite-347.htm.

Upper management: A group of persons in charge of the highest executive management of an organization. Membership of this group is determined by the governance structure of the organization. While it is envisaged that the upper management usually is a group, the head of the organization is the one person at the top of the organization with ultimate responsibility for ensuring that the organization complies with relevant legislation.

[5] See **Committee of Sponsoring Organizations (COSO)**, www.coso.org

IV.B. Structures and processes

The structures and the processes of pharmacovigilance audits in Lebanon has to be implemented following the Good Pharmacovigilance Practice (GVP) for Lebanon. This module explains multiple items that shall be considered in audit implementation such as: PV audit and its objectives, the risk-based approach to PV audits, and quality system and record management practices.

IV.B.1. Pharmacovigilance audit and its objective

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

In general, an audit is a systematic, disciplined, independent, and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control, and governance processes[6,7].

Audit evidence consists of records, statements, or other information that are relevant to the audit criteria and are verifiable. Audit criteria are, for each audit objective, the standards of performance and control against which the auditee and its activities will be assessed. In the context of pharmacovigilance, audit criteria should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the legislation and guidance.

IV.B.2. The risk-based approach to pharmacovigilance audits

A risk-based approach is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome and/or likelihood of non-detection by other methods. The risk-

[6] Benchmarking, reviews of qualifications, risk assessment questionnaires, surveys, or other activities in which evidence of fulfilment of pharmacovigilance requirements is not independently obtained and evaluated, would not be regarded as an audit
[7] EU GVP annex 1 definitions referencing the ISO 19011 for the definition: https://www.iso.org/obp/ui/#iso:std:iso:19011:ed-3:v1:en

based approach to audits focuses on the areas of highest risk to the organization's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

- strategic level audit planning resulting in an audit strategy (long-term approach), which should be endorsed by upper management;
- tactical level audit planning resulting in an audit program, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that program; and
- operational level audit planning resulting in an audit plan for individual audit engagements, prioritizing audit tasks based on risk and utilizing risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system [see IV.B.2.3.2.]

Risk assessment should be documented appropriately for the strategic, tactical, and operational planning of pharmacovigilance audit activity in the organization (see IV.B.2.1., IV.B.2.2. and IV.B.2.3. respectively).

IV.B.2.1. Strategic level audit planning

The audit strategy is a high-level statement of how the audit activities will be delivered over a period of time, longer than the annual program, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit program is based.

The audit strategy should cover the governance, risk management, and internal controls of all parts of the pharmacovigilance system including:

- all pharmacovigilance processes and tasks;
- the quality system for pharmacovigilance activities;
- interactions and interfaces with other departments, as appropriate; and

- pharmacovigilance activities conducted by affiliated organizations or activities delegated to another organization (e.g. regional reporting centers, MAH affiliates, or service providers, such as contract organizations and other vendors).

This is a non-prioritized, non-exhaustive list of examples of risk factors that could be considered for a risk assessment:

- changes to legislation and guidance;
- major re-organization or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for marketing authorization holders, this may lead to a significant increase in the number of products for which the system is used);
- change in key managerial function(s);
- risk to the availability of adequately trained and experienced pharmacovigilance staff, e.g., due to significant turnover of staff, deficiencies in training processes, re-organization, and increase in volumes of work;
- significant changes to the system since the time of a previous audit, e.g., introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities to address new or amended regulatory requirements;
- first medicinal product on the market (for a marketing authorization holder);
- medicinal product(s) on the market with specific risk minimization measures or other specific safety conditions, such as requirements for additional monitoring;
- criticality of the process, e.g.:
    - for national competent authorities: how critical is the area/process to the proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;
    - for marketing authorization holders: how critical is the area/process to the proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or service provider, the marketing authorization holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or service provider on behalf of the marketing authorization holder, in addition to considering the other factors included in this list;
- outcome of previous audits, e.g., has the area/process ever been audited (if not, then this may need to be prioritized depending on criticality); if the area/process has previously been audited, the audit

findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;

- identified procedural gaps relating to specific areas/processes;
- other information relating to compliance with legislation and guidance, for example:
  - for national competent authorities: information from compliance metrics of complaints, and from external sources (e.g., audits/assessments of the national competent authority that may be conducted by external bodies);
  - for marketing authorization holders: information from compliance metrics of inspections (see Module III), from complaints, and from other external sources (e.g., audits);
- other organizational changes that could negatively impact on the area/process, e.g., if a change occurs to a support function (such as information technology support), this could negatively impact upon pharmacovigilance activities.

IV.B.2.2. Tactical level audit planning

An audit program is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long-term audit strategy. The audit program should be approved by upper management with overall responsibility for the operational and governance structure.

The risk-based audit program should be based on an appropriate risk assessment and should focus on:

- the quality system for pharmacovigilance activities;
- critical pharmacovigilance processes (see, for example, Module I);
- key control systems relied on for pharmacovigilance activities;
- areas identified as high risk, after controls have been put in place or mitigating action taken.

The risk-based audit program should also take into account historical areas with insufficient past audit coverage and the high-risk regions identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

The audit program documentation should include a brief description of the plan for each audit to be delivered, including an outline of the scope and objectives.

The rationale for the timing, periodicity, and scope of the individual audits that form part of the audit program should be based on the documented risk assessment. However, risk-based pharmacovigilance audit(s) should be performed at regular intervals, which are in line with national legislative requirements.

Changes to the audit program may happen and will require proper documentation.

IV.B.2.3. Operational level audit planning and reporting

IV.B.2.3.1. Planning and fieldwork

The organization should ensure that written procedures are in place regarding the planning and conduct of individual audits that will be delivered. Timeframes for all the steps required for the performance of an individual audit should be settled in the relevant audit-related procedures, and the organization should ensure that audits are conducted per the written procedures, in line with this GVP Module.

Individual pharmacovigilance audits should be undertaken in line with the approved risk-based audit program (see IV.B.2.2). When planning individual audits, the auditor identifies and assesses the risks relevant to the area under review and employs the most appropriate risk-based sampling and testing methods, documenting the audit approach in an audit plan.

IV.B.2.3.2. Reporting

The findings of the auditors should be documented in an audit report and should be communicated to management in a timely manner. The audit process should include mechanisms for communicating the audit findings to the auditee and receiving feedback, and reporting the audit findings to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings should be reported in line with their relative risk level and should be graded to indicate their relative criticality to risks impacting the pharmacovigilance system, processes, and parts of processes. The grading system should be defined in the description of the quality system for pharmacovigilance, and should take into consideration the thresholds noted below, which would be used in further reporting under the legislation as set out in section IV.C.2:

- **critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety, or well-

being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.

- **major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.

- **minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.

Issues that need to be urgently addressed should be communicated in an expedited manner to the auditee management and the upper management.

IV.B.2.4. Actions based on audit outcomes and follow-up of audits

Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the pharmacovigilance system. Corrective and preventive actions to address critical and major issues should be prioritized. The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on the nature of the findings and the planned action(s).

The management of the organization is responsible for ensuring that the organization has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.

Upper management and those charged with governance should ensure effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis, proportionate to the planned actions, to upper management.

Evidence of completion of actions should be recorded in order to document that issues raised during the audit have been addressed.

Capacity for follow-up audits should be foreseen in the audit program. They should be carried out as deemed necessary, in order to verify the completion of agreed actions.

IV.B.3. Quality system and record management practices

IV.B.3.1. Competence of auditors and quality management of audit activities

IV.B.3.1.1. Independence and objectivity of audit work and auditors

The organization should assign specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent. The organization's management should ensure this independence and objectivity in a structured manner and document this.

In line with EU implementing legislation, marketing authorization holders shall perform regular audits of the pharmacovigilance quality system at risk-based intervals to ensure compliance with requirements and to determine its effectiveness. Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance audits, and communicating audit results. The main reporting line should be to the upper management with overall responsibility for the operational and governance structure that allows the auditor(s) to fulfill their responsibilities and to provide an independent, objective audit opinion.

Audits shall cover all pharmacovigilance activities for a defined period and verify their conformity with established policies, processes, and procedures of the quality system.

Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and the person responsible for pharmacovigilance; however, auditors should maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made.

Audits shall be conducted by individuals who have no direct involvement in, or responsibility for, the matters or processes being audited.

Objectivity requires auditors not to subordinate their judgment on audit matters to that of others.

IV.B.3.1.2. Qualifications, skills, and experience of auditors and continuing professional development

Auditors should demonstrate and maintain proficiency in terms of the knowledge, skills, and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience, and training, and, as a team, should cover knowledge, skills, and abilities in:

- audit principles, procedures, and techniques;
- applicable laws, regulations, and other requirements relevant to pharmacovigilance;
- pharmacovigilance activities, processes and system(s);
- management system(s);
- organizational system(s).

IV.B.3.1.3. Evaluation of the quality of audit activities

Evaluation of audit work can be undertaken through ongoing and periodic assessment of all audit activities, auditee feedback, and self-assessment of audit activities (e.g., quality assurance of audit activities, compliance to code of conduct, audit program, and audit procedures).

IV.B.3.2. Audits undertaken by outsourced audit service providers

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization (i.e., within the national competent authority or marketing authorization holder). Where the organization decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements based on this GVP module and perform pharmacovigilance audits:

- the requirements and preparation of the audit risk assessment, the audit strategy, the audit program, and individual engagements should be specified to the outsourced service providers by the organization, in writing;
- the scope, objectives, and procedural requirements for the audit should be specified to the outsourced service provider by the organization, in writing;

- the organization should obtain and document assurance of the independence and objectivity of outsourced service providers;
- the outsourced audit service provider should also follow the relevant parts of this GVP module.

IV.B.3.3. Retention of audit reports

Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in Module I.

IV.C. Operation in Lebanon: Pharmacovigilance audit policy framework

IV.C.1. Requirement to perform an audit for Marketing authorization holders in Lebanon

The marketing authorization holder in Lebanon is required to perform regular risk-based audit(s) of their pharmacovigilance system, including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements. The dates and results of audits and follow-up audits shall be documented.

See IV.C.2 for further details of the requirements for audit reporting by the marketing authorization holder.

IV.C.1.1. The national qualified person for pharmacovigilance (QPPV)/and the local safety responsible (LSR)

The responsibilities of the National QPPV and LSR for audit are provided in Module I. Furthermore, the national QPPV and LSR should receive pharmacovigilance audit reports and provide information to the auditors relevant to the risk assessment, including knowledge of the status of corrective and preventive actions.

The national QPPV and LSR should be notified of any audit findings relevant to the pharmacovigilance system, irrespective of where the audit was conducted.

For multinational marketing authorization holders, international companies, and other companies, the Local Safety Responsible (LSR) should receive pharmacovigilance audit reports and provide information to the auditors relevant to the risk assessment, including knowledge of the status of corrective and preventive actions at the national level. Furthermore, the concerned LSR should be notified of any audit findings relevant to the pharmacovigilance system in Lebanon, where the audit was conducted.

IV.C.2. Requirements for audit reporting by the marketing authorization holder in Lebanon

The marketing authorization holder shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF) (see Module II). Based on the audit findings, the marketing authorization holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented. Once the corrective and preventive actions have been fully implemented, the note may be removed. Objective evidence is required in order for any note of audit findings can be removed from the pharmacovigilance system master file (see Module II).

The marketing authorization holders should ensure that a list of all scheduled and completed audits is kept in the annex to the pharmacovigilance system master file and that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies. The dates and results of audits and follow-up audits shall be documented.

IV.C.3. Confidentiality

Documents and information collected by the internal auditor should be treated with appropriate confidentiality and discretion, and also respect national legislation on the protection of individuals concerning the processing of personal data and the free movement of such data.