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3 Guideline on good pharmacovigilance practices (GVP)

4 Module IV – Pharmacovigilance audits

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6 Comments should be provided using this template. The completed comments form should be sent to
7 gvp@ema.europa.eu.

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IV.A. Introduction

Following the entry into force of the new legislation on pharmacovigilance in July 2012, there is a requirement for marketing authorisation holders, competent authorities in the Member States and the European Medicines agency (the Agency) to perform audits of their pharmacovigilance systems [DIR Art 101(2), Art 104(2), REG Art 28f], including risk based audits of their quality systems [IR Art 13 (1), Art 17 (1).]

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 minimum requirements of the pharmacovigilance systems and the quality system are set out in the Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council (IR). Risk-based audits of the pharmacovigilance system contain all areas listed in Directive 2001/83/EC (DIR) and Regulation (EC) 726/2004 (REG). The specificities of the risk-based audits of the quality system [for pharmacovigilance activities] are as described in the Implementing Measures [IR Art 8,10, 11,12,13(1) for marketing authorisation holders, and IR Art 8,14,15,16,17(1) for national competent authorities and the Agency.]

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 GVP.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable 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, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity. This Module is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonisation, 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 standardisation organisations*[1] and support a risk-based approach pharmacovigilance audits.

Section IV.B. outlines the general structures and processes that should be followed to identify the most appropriate pharmacovigilance audit engagements and describes the steps which can be undertaken by marketing authorisation holders, competent authorities in Member States and the European Medicines Agency, to plan, conduct and report upon an individual pharmacovigilance audit engagements. This Section also provides an outline of the general quality system and record management practices for pharmacovigilance audit processes.

Section IV.C. provides and outline of the operation of the EU network in respect of pharmacovigilance audits.

[1] More details regarding **The Institute of Internal Auditors** (IIA) www.theiia.org; the **International Organisation for Standardisation** (ISO) www.iso.org; **Information Systems Audit and Control Association** (ISACA) www.isaca.org; **The International Auditing and Assurance Standards Board** (IAASB) www.ifac.org; **The International Organisation of Supreme Audit Institutions** (INTOSAI) www.issai.org.

Note for public consultation: Terms marked with a star (*) are included in a glossary of terms that defines terms and abbreviations in an annex at the end of the Module. After public consultation, this annex will be deleted, as these definitions as finalised will be incorporated in the GVP Annex Definitions

IV.B. Structures and processes

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 it objectively to determine the extent to which the criteria are fulfilled, contributing to the improvement of risk management, control and governance processes. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and 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 high-risk areas, 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-based approach to audits focuses on the areas of highest risk to the organisation'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 is assessed at the following stages:

- strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by senior management;
- tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; and
- operational level audit planning resulting in an audit plan for individual audit engagements, prioritising audit tasks based on risk and utilising 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.2.3.1.]

In order to implement a risk-based approach to pharmacovigilance audits, the auditors should carry out and document risk assessments as a basis for the strategic, tactical and operational planning of pharmacovigilance audit activity in their organisation (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 programme, usually for a period of 3-5 years. The audit strategy includes a list of all possible audits that could be performed and an assessment of risk, resources and training

needs. The audit strategy is used to outline the areas highlighted for audit, the audit themes as well as the methods and assumptions on which the audit programme 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;
- pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties).

This is a non-prioritised, non-exhaustive list of examples of risk factors that could be considered for the purposes of a risk assessment at the strategic audit planning level:

- changes to legislation and guidance;
- mergers, major re-organisation or other re-structuring of the pharmacovigilance system, (specifically for marketing authorisation 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 availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, recent re-organisation, recent 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 in order to address new or amended regulatory requirements;
- first medicinal product on the market (for a marketing authorisation holder);
- medicinal product(s) on the market with specific risk minimisation measures or other specific safety conditions such as requirements for additional monitoring;
- criticality of the process, e.g.:
  - for competent authorities: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;
  - for marketing authorisation holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorisation holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by affiliate or third party on behalf of the marketing authorisation 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 prioritised 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 competent authorities: information from compliance* metrics (as described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC), from complaints, from external sources, e.g. audits/assessments of the competent authority conducted by external bodies;
  - for marketing authorisation holders: information from compliance* metrics (as described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC), from inspections see Module III, from complaints, from other external sources, e.g. audits;
- other organisational 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 programme is a set of one or more audits planned for a specific timeframe, normally for a year. The audit programme should be approved by the head of the organisation.

The risk-based audit programme 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 and IR Art 11, 15);
- 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 programme should also take into account areas with insufficient past audit coverage, and high risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

The audit programme document should include a brief description of the plan for each audit to be delivered, including its scope and objectives.

The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme should be based on the documented risk assessment. However, risk-based pharmacovigilance audit(s) should be performed at regular intervals to assure that the system complies with the legislative requirements.

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

IV.B.2.3.1. Planning and fieldwork

The organisation 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 organisation should ensure that audits are conducted in accordance with the written procedures.

Individual pharmacovigilance audits should be undertaken in line with the approved risk-based audit programme (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* and audit recommendations* of the auditors should be documented in an audit report and 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* and audit recommendations to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings and audit recommendations* should be reported in line with their relative risk level and should be graded in order 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 legislation and guidelines. The audit recommendation aims at introducing mitigating action that addresses the risk of the critical audit finding so that it is not detrimental at the level assessed anymore; immediate action is required;
- **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 legislation and guidelines which is however not considered serious. The audit recommendation aims at introducing mitigating action that addresses the risk of the major audit finding so that it is not detrimental at the level assessed anymore; prompt action is required;
- **mino**r 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. The audit recommendation aims at introducing mitigating action that addresses the risk of the minor audit finding so that it is not detrimental at the level assessed anymore; action within a reasonable timeframe is required.

Serious concerns that need to be urgently addressed should be communicated in an expedited manner to the auditee*'s management and the senior management.

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

The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the audit recommendations* arising from pharmacovigilance audits, including the preparation of an action plan.

Senior management and those charged with governance, should ensure that effective action is implemented to address the audit findings and audit recommendations* arising from pharmacovigilance audits or formally accept the risk of not taking action. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis to senior 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 programme. They should be carried out as deemed necessary, in order to verify the completion of agreed actions. [IR Art 13(2), Art 17(2)]

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 organisation should assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent and separate from routine quality control* activities relating to pharmacovigilance.

In order to be independent, audits should be conducted by those who have no actual or potential conflicts of interest and who are not operationally involved in the activities to be audited. [IR Art 13(1)] The organisation's management should ensure this independence and objectivity in a structured manner and document this.

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 level within the organisation that allows the auditor(s) to fulfil their responsibilities (for example the auditor(s) may functionally report to the head of the organisation or an oversight body like an audit committee or management board).

Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with 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. Objectivity requires auditors not to subordinate their judgement 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. 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);
- organisational system(s).

Adequate training for auditors should also be considered by the organisation (see Module I).

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

Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, auditee* feedback and self-assessment of audit activities.

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 organisation (i.e. within the Agency, competent authority or marketing authorisation holder). Where the organisation decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP module and perform pharmacovigilance audits:

- the requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements should be specified to the outsourced service providers, by the organisation, in writing;
- the scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organisation, in writing;
- the organisation 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.C. Operation of the EU network

IV.C.1. Pharmacovigilance audit policy framework and organisational structure

IV.C.1.1. Marketing authorisation holders in the EU

IV.C.1.1.1. Requirement to perform an audit

The marketing authorisation holder in the EU is required to perform regular risk-based audit(s) of their pharmacovigilance system [DIR Art 104(2)], including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements [IR Art 8,10,11,12,13(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)]

See IV.C.2. for further details of the requirements for audit reporting by the marketing authorisation holder to competent authorities and the Agency.

IV.C.1.1.2. The qualified person responsible for pharmacovigilance in the EU (QPPV)

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

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

IV.C.1.2. Competent authorities in Member States and the European Medicines Agency

IV.C.1.2.1. Requirement to perform an audit

The Agency shall perform regular independent audits of its pharmacovigilance tasks [REG Art 28f] and competent authorities in Member States shall perform a regular audit of their pharmacovigilance system [DIR Art 101(2)]. Included in their obligation to perform audits of their pharmacovigilance

system/tasks, competent authorities in the Member States and the Agency shall perform risk-based audits of the quality system as well, at regular intervals according to a common methodology to ensure that the quality system complies with the requirements [IR Art 8,14,15,16,17(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 17(2)].

IV.C.1.2.2. Common methodology

In order to have a useful audit system, all audits at the competent authorities in the Member States and the European Medicines Agency should have a common ground in terms of methodology. This should ensure harmonised planning, implementation and reporting by every competent authority in Member States and at the Agency.

IV.C.1.2.3. The Pharmacovigilance Risk Assessment Committee (PRAC)

The mandate of the Pharmacovigilance Risk Assessment Committee (PRAC) shall cover all aspects of the risk management of the use of medicinal products for human use, having due regard to the design and evaluation of pharmacovigilance audits [REG Art 61a(6)].

IV.C.2. Requirements for audit reporting in the EU

IV.C.2.1. Reporting by the marketing authorisation holder

The marketing authorisation holder shall place a note concerning the main audit findings* and audit recommendations, including critical and major audit findings/audit recommendations of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF). Based on the audit findings*and audit recommendations, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented. Once the corrective and preventative actions have been fully implemented, the note may be removed [DIR Art 104(2), IR Art 13(2)]. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file(see Module II).

The marketing authorisation holders should ensure 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 [IR Art 13(2)].

IV.C.2.2. Reporting by competent authorities in Member States and the Agency

Competent authorities in Member States, and the Agency should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies.

Competent authorities in Member States shall report the results [of their pharmacovigilance system audits] to the Commission on 21 September 2013 at the latest and then every 2 years thereafter [DIR Art 101(2)].

The Agency shall report the results [of its pharmacovigilance system audits] to its Management Board on a 2-yearly basis [REG Art 28f].

The reports to the European Commission will follow an agreed format.

IV.C.3. Confidentiality

Documents and information collected by the internal auditor will be treated with appropriate confidentiality and discretion, and also respect Directive 95/46/EC [Regulation (EC) No. 45/2001 for Community institutions and bodies] and national legislation on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

IV.C.4. Transparency

The European Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter [REG Art 29] and on the performance of pharmacovigilance tasks by the competent authorities in Member States on 21 July 2015 at the latest and then every 3 years thereafter [DIR Art 108(b)].

GLOSSARY OF TERMS

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 (ISO 19011 (3.1[2]).

Audit finding(s): results of the evaluation of the collected audit evidence against audit criteria (ISO19011 (3.4)[2]).

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

[Audit] recommendation(s): Describe the course of action management might consider to rectify conditions that have gone awry, and to strengthen weaknesses in systems of [management] control. [Audit] recommendations should be positive and as specific as possible. They should also identify who is to act on them. (Sawyer, L.B. , Dittenhofer M.A. (2003), Sawyer's Internal Auditing, 5th Edition, The IIA Research Foundation, p.358)

Auditee: [entity] being audited (ISO 19011 (3.7) [2]).

Benchmarking of the European Medicines Agencies (BEMA): HMA (Joint Human and Veterinary) has established a benchmarking programme among the human and veterinary medicines agencies with the broad aim to contribute to the development of a world-class medicines regulatory system based on a network of agencies operating to best practice standards. A Steering Group has been established to develop the programme and oversee its roll-out.

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, organises, 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*[4]).

Finding(s): see Audit findings

International Auditing Standards: Standards issued by International Auditing Standardisation Organisations*.

International Auditing Standardisation Organisations: 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 Organisation for Standardisation** (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 Organisation of Supreme Audit Institutions (INTOSAI) can be found at http://www.issai.org/composite-347.htm

Organisation: unless otherwise specified, reference to "organisation" is deemed to refer to Marketing Authorisation Holder or National Competent Authority or EMA.

Standards: see International Auditing Standards.

[2] the **International Organisation for Standardisation** (ISO) www.iso.org
[3] **The Institute of Internal Auditors** (IIA) www.theiia.org