Εσωτερικοί έλεγχοι (Audits) στη Φαρμακοεπαγρύπνηση

Νομοθεσία (GVP) για ελέγχους

Ερριέττα Οικονόμου, Creative Pharma Services

Νομοθεσία (GVP) για ελέγχους

GVP Module I	GVP Module II	GVP Module IV
Pharmacovigilance systems and their quality systems	**Pharmacovigilance system master file**	**Pharmacovigilance audits**
22 Jun 2012	Rev 2 – 28 Mar 2017	Rev 1 - 3 August 2015
Describes Audit as a **component of the PV Quality System** in terms of monitoring its **performance** and **effectiveness** and defines the responsibility of the "**Management**" (management responsible for the matters audited & EUQPPV) to ensure they are conducted.	Describes the aspects of the audit **programme and its outputs** which must be **summarised in the PSMF**. PSMF shall contribute to the **appropriate planning and conduct** of audits by the applicant or MAH(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by national competent authorities.	Describes the "mechanics" of **planning, conducting and responding** to audits. **Audit criteria** should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the legislation and guidance.

Module I: Pharmacovigilance systems and their quality systems

I.B.12. Monitoring of the performance and effectiveness of the PV system and its quality system

The process should include:

- Reviews of the systems by those responsible for management
- Audits
- Compliance monitoring
- Inspections
- Evaluating the effectiveness of actions taken with medicinal products

- Risk-based audits of the quality system shall be performed at **regular intervals**
- Audits of the quality system should include audit of the PV system which is the **subject of the quality system**
- In relation to the PV system of a MAH, a **report** shall be drawn up on the results for each quality audit and any follow-up audits be sent to the **management responsible** for the matters audited
- The report should include the results of audits of **organisations or persons** the marketing authorisation holder has delegated tasks to, as **these are part of the MAH's PV system**
- As a consequence of the monitoring of the performance and effectiveness of a PV system and its quality system (including the use of audits), **corrective and preventive measures** should be implemented when deemed necessary

Module II: Pharmacovigilance System Master File

PSMF – II.B.4.7 Quality System

- A description of the approach used to **plan audits** and the **reporting mechanism** and **timelines** should be provided
- Current **list of the scheduled and completed audits** (maintained in the annex) – (cover a rolling 5 year period, Audit date(s), Scope and completion status)
- Note on audits where **significant findings** are raised - those that fulfil the EU criteria for major or critical findings
- Audit report must be documented **within the quality system**

- In the PSMF a brief description of the CAPA associated with the **significant finding**, the date it was identified and the anticipated resolution date(s), should be entered
- Audits associated with **unresolved notes** should be identified in the annex listing
- "Note" can be removed once the corrective action is demonstrated to be **completed**
- Addition/amendment or removal of the notes must be **recorded in the logbook**
- The PSMF should also describe the process for recording, managing and resolving **deviations from the quality system**

GVP Module IV: Pharmacovigilance audits

Describes the requirements for PV Audit in terms of:

1. Planning
2. Reporting
3. Post-audit actions and follow-up
4. Competence of auditors and QM of audit activities
5. Outsourcing audit activities

2. Reporting

- **Findings and recommendations** should be documented in an **audit report** and communicated to management in a timely manner, and the auditee
- Findings should be graded: critical, major, minor

Risk: 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.

1. Planning → risk-based approach

- Strategic Level Audit Planning: audit activities over a period of time, longer than the annual programme, usually for a **period of 2-5 years**
- Tactical Level Audit Planning: set of one or more audits planned for a specific timeframe, normally **for a year** in line with the long term audit strategy
- Operational Level Audit Planning: **individual audit engagements** identified and assessed according to the risks relevant to the area under review

GVP Module IV: Pharmacovigilance audits

3. Post-audit actions and follow-up

- **Immediate Action, Prompt Action, Action Within A Reasonable Timeframe**.. Appropriate timelines should be in line with the **relative risk** to the pharmacovigilance system.
- Corrective and preventive actions to address **critical and major issues** should be prioritised.
- **Management should ensure there is a mechanism in place to adequately address issues arising from PV audits** (Audit response/CAPA, Root cause and impact analysis, Appropriate timeframes)
- **Implementation of agreed actions should be monitored**…
- **Progress communicated periodically to senior management**
- **Evidence of completed actions should be recorded**

4. Competence of auditors and QM of audit activities

- **Competence of Auditors** (Qualifications and skills, Training)
- **Independence and objectivity of audit work** (Conflict of interest, No "interference" in determining audit scope, Unbiased attitude, belief in work product, no quality compromises
- **Evaluation of audit activities** (Assessment of all audit activities, auditee feedback and self-assessment of audit activities)

5. Outsourced audit service providers

- The following should be specified
  - Audit requirements regarding risk assessment, strategy, programme and individual engagements
  - Scope, objectives and procedural requirements
- Independence and objectivity must be assured
- GVP must be followed

	Types of Audits (one type of each category should be fulfilled)
1	**System or process audit** Case processing, aggregate reports, EEA QPPV, etc. Key processes / procedures which compromise the global PV system, SDEA / contracts management oversight
2	**Internal** • Global Pharmacovigilance System Audit • Subsidiary audit (Affiliates/operating companies) • Department audit
	External • Business / License Partner Audit (e.g. Development, Marketing Partner, Manufacturer, Distributor, Vendor) - At Distributor or vendor sites safety department. Generally has a limited scope (as per Business / License Agreement) • Service Provider Audit (Third parties with specific delegated PV responsibilities such as literature review, medical information etc.)
3	**Routine audit** Audits scheduled in advance as part of audit programmes
	For-cause audits (triggered) For cause audits are more likely to focus on specific PV processes or to include an examination of identified compliance issues and their impact for a specific product
	Verification audit Re-visiting previously conducted audit to verify completion of agreed corrective action plans focused on the outcome of the previous audit

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Εσωτερικοί έλεγχοι (Audits) στη Φαρμακοεπαγρύπνηση
Προετοιμασία του ελεγχόμενου για τη διεξαγωγή ενός Audit

Ελεονώρα Σαρίκου, GlaxoSmithKline

Be always prepared for a PV audit!

Ensure that:

- ✓ A contact person for pharmacovigilance is nominated to the Competent Authority (EU and local QPPV)
- ✓ An appropriate quality management system is in place as a basis for an effective PV system – including up-to-date SOPs and PV training
- ✓ All potential sources are being monitored for ICSRs, including but not limited to market research programs, medical information, product quality complaints, literature, company sponsored internet sites and social media, clinical trials etc.
- ✓ Periodically monitoring of the applicable legislation
- ✓ Safety Data Agreements are in place with required partners
- ✓ Timely reporting of required PV information to regulatory authorities, e.g., ICSRs, periodic reports
- ✓ Management monitoring/QC checks/Self-inspections /Internal Audit Plan is in place

Audit Plan - Pre-audit information request

- An initial email notice is sent to the auditee to explain the scope of the audit & confirm the audit dates.
- One month prior to the audit, a list with all the requested information is sent to the auditee

The duration depends on the scope of the audit and can be between 2 to 4 working days.

- PSMF
- Organograms –Structure of the PV Organization
- List of activities & responsibilities
- Territories of responsibilities
- Local Legislation
- Local SOPs / Guidances / Working Documents
- Case reporting process flow
- Product list
- Local SmPCs & PILs updates
- List of contractual partners (Service Agreements, SDEAs)
- Clinical Trials, NPPs, CUPs, IISs List
- Market Research, Digital Media, Patient Support Programs, Health Outcome Studies
- Locally managed computer systems & databases
- Aggregate reports
- List of Medical Information Requests
- DHPC letters
- Risk Management Plans & Educational Materials

During the on-site Audit

- Opening meeting / Introduction
- Interviews: GM, Country Medical Director, Pharmacovigilance staff, Medical Information, Sales reps & other company employees, Regulatory Affairs, Quality & Compliance staff, Call center, Externally Contracted Parties (e.g. CROs, Vendors, Licensing Partners)
- Review of collection, processing, management, quality control, follow-up and timely transmission of individual case safety reports (ICSRs) from any source & Aggregate reports
- Reporting metrics for ICSR and Aggregate reports
- Literature process review
- PV training process/ Training plan and Training record review
- Medical Information process (Call Center, Out of hours process) and collaboration with PV
- Quality Complaints Handling and collaboration with PV department
- Regulatory Affairs & Interface with PV
- Reconciliations between local safety department and other departments/ partners that obtain safety data
- Archiving / Record retention
- Business Continuing Plan for critical pharmacovigilance processes
- Internal audit process review/ CAPA status
- Closing Meeting / Initial presentation of audit findings

Post –Audit Actions

- Findings and recommendations are documented in the Audit report (Minor, Major, Critical)

  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.

- Corrective And Preventive Actions (CAPAs) to address the findings are also included in the Audit report with specific timelines for completion
- Evidence of completion of CAPAs should be recorded in order to document that issues raised during the audit have been addressed.
- The audit is closed when applicable CAPAs have been completed.

Common findings

- All reported cases from all sources not received or reported by the PV department
- Late ICSR & Aggregate reporting
- Source documents not retained or source documents are not accurately translated or transcribed to the safety database
- Deficiency in identifying adverse events from quality complaints and medical enquiries
- Inadequate reconciliation between local safety department and other departments that obtain safety data (Medical Information, Quality complaints, Licensing partners)
- Lack of communication of local label changes to the appropriate staff after approval or delay in implementation
- SOPs do not accurately reflect current process
- SDEAs: No SDEA in place, Safety not involved in development of contract or SDEA, Lack of company oversight for SDEA, Roles and responsibilities of each party is not clarified in the SDEA
- PV training not provided to all personnel
- Signal detection-Inadequate documentation to show: Decisions taken and who was involved, Rationale for frequency review, At the time of PSUR production will not be appropriate for all products, Validation issues e.g. when a new system is implemented

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Εσωτερικοί Έλεγχοι στη Φαρμακοεπαγρύπνηση

σχεδιασμός-κριτήρια-προκλήσεις-βήματα-ευρήματα

Ανδρέας Κουρβετάρης

Senior Safety Manager, Zeincro Hellas S.A.

Σχεδιασμός ελέγχων

Κριτήρια για την εκτίμηση κινδύνου

- Κίνδυνος για τη δημόσια υγεία
- Κίνδυνος για την εταιρεία
- Σύστημα ποιότητας και ωρίμανση αυτού
- Εκπαίδευση
- Υπεργολαβίες
- Μεταβολές στο προσωπικό
- Αλλαγές στη νομοθεσία
- Προηγούμενοι έλεγχοι/επιθεωρήσεις
- Δείκτες συμμόρφωσης
- Όγκος περιστατικών
- Όγκος πωλήσεων
- Προϊόντα (είδη, πλήθος…)

Προκλήσεις που αντιμετωπίζονται με συνεργάτες-προμηθευτές:

- **Απροθυμία συνεννόησης λόγω άγνοιας**
- **Κατανόηση SDEA**
- **Απουσία συστήματος ποιότητας**
- **Απουσία προσωπικού σχετικού με τη συντήρηση συστήματος ποιότητας**
- **Ελλείψεις στο σύστημα**
- **Ελλείψεις στις εκπαιδευτικές διαδικασίες**
- **Εμπόδια λόγω γλώσσας/κουλτούρας**

Βήματα για την επιτυχή ολοκλήρωση εσωτερικών ελέγχων

- Κοινοποίηση ελέγχου
- Μελέτη/Έρευνα
- Audit Plan/Audit Agenda
- Έλεγχος
- Καταγραφή (Audit Report)

GVP IV Rev 1 (page 5, footnote 3): "Benchmarking, review of qualifications, risk assessment questionnaires, surveys or other activities in which evidence of fulfillment of pharmacovigilance requirements is not independently obtained and evaluated, would not be regarded as an audit."

Τα ευρήματα (**findings: critical, major, minor**) και οι συστάσεις (recommendations) θα πρέπει να καταγράφονται σε μια αναφορά ελέγχου (audit report) και να **κοινοποιούνται**:

- **στον ελεγχόμενο**
- **στους υπευθύνους** για τη φαρμακοεπαγρύπνηση (περιλαμβάνεται: EU-QPPV) και τα σχετικά μέρη

αν υπάρχουν ευρήματα που εγείρουν **σοβαρή ανησυχία**, πρέπει να κοινοποιούνται άμεσα στη **διοίκηση** και τον ελεγχόμενο.

Βήματα για την επιτυχή ολοκλήρωση εσωτερικών ελέγχων

- Root cause/Impact analysis
- Audit report response – CAPA
- Χρονοδιαγράμματα
- Παρακολούθηση επίλυσης ευρημάτων και τεκμηρίωση
- (Περιοδική) ενημέρωση της διοίκησης
- Follow up έλεγχοι – Κυκλικότητα?
- Επανεκτίμηση των κριτηρίων για την εκτίμηση κινδύνου

Ευρήματα επιθεωρήσεων σχετικά με τους εσωτερικούς ελέγχους

- Έλλειψη ελέγχων και σχεδιασμού ελέγχων
- Ανεπαρκής κάλυψη (π.χ. δεν καλύπτονται service providers)
- Παράβλεψη δραστηριοτήτων από τους ελέγχους (π.χ. ανίχνευση σήματος, RSI updates)
- Ελεγκτές PV χωρίς αντίστοιχες γνώσεις ή εμπειρία ή ακατάλληλοι λόγω του οργανογράμματος
- Η εκτίμηση κινδύνου να αξιολογείται διαφορετικά από τους επιθεωρητές
- Έλλειψη τεκμηρίωσης σχετικά με το σχεδιασμό ελέγχων

Ευχαριστώ!

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