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Managing Pharmacovigilance Audits and Inspections

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Audit - Introduction

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.

Objectives

- ensure the goals are achieved (safety of patients is maintained)
- identify risk and areas for improvement and
- ensure compliance with company procedure and regulatory body requirements

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Important Definitions

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

Risk-based approach – The use of technique(s) to determine the areas of risk

Audit programme – A set of one or more audits planned for a specific timeframe, normally for a year

Audit plan: Description of activities and arrangement for an individual audit

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Risk Based Approach

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.

In the context of PV, the risk to public health is of prime importance.

Risk can be assessed at the following stages:

- ***Strategic*** **Level Audit Planning**
  - Long-term audit strategy endorsed by upper management
- ***Tactical*** **Level Audit Planning**
  - Audit programme, generally for 1 year, along with the objectives and scope of audits
- ***Operational*** **Level Audit Planning**
  - Audit plan for individual audit engagements

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Strategic Level Audit Planning

- ❑ Provides information on the audit activities to be delivered over 2-5 years
- ❑ Includes a list of audits that could reasonably be performed
- ❑ Outlines areas highlighted for audit, audit topics as well as the audit programme's methodology and assumptions

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*Strategic Level Audit Planning: F*actors for Risk Assessment*

Changes

- legislation and guidance;
- major re-organization or other re-structuring in relation to PV or organization;
- change in key managerial function(s);
- significant changes to the system since the time of a previous audit such as introduction of a new database

Product related

- first medicinal product on the market;
- marketed product(s) with specific requirements such as risk minimization measures;

Resource and process related

- criticality of the process;
- availability of adequately trained and experienced PV staff
- outcome of previous audits;
- identified procedural gaps relating to specific areas/processes;

* Non-prioritised, non-exhaustive list of examples

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Tactical Level Audit Planning

Prepare Audit programme:

- In line with the long-term audit strategy and approved by upper management
- Describe plan for each audit to be delivered including scope and objectives

Risk-based:

- Rationale for timing, periodicity and scope of the individual audits based on documented risk assessment
- Focus on:
  - the quality system for PV activities
  - critical PV processes
  - key control systems relied on for PV activities
  - areas identified as high risk, after controls have been put in place or mitigating action taken

Audit programme: *set of 1 or more audits in a specific timeframe (usually a year)*

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Operational Level Audit Planning

- Planning:
  - Written procedures for planning and conduct of individual audits
  - Timeframes should be set for all steps
  - Individual PV audits:
    - should be in line with approved risk-based audit programme
    - employ most appropriate risk-based sampling and testing methods
    - document the audit approach in an audit plan
- Reporting:
  - *Next Slide*

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Audit Report

Issue within defined timelines

Include Executive Summary

Describe objectives and scope of audit

Observations:

Clear description of conditions observed	Reference or criteria as the basis for the observation	Quantification / Examples for context as applicable	Assessment of cause and effect	Grading (Critical, Major, Minor)	Process / Quality improvement opportunities

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Grading System for Audit Findings

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.

Guideline on good pharmacovigilance practices (GVP) – Module IV (Rev 1)

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Quality Management of Audit Activities

Organization should assign the specific responsibilities for the PV audit activities

PV audit activities should be independent

Auditors should be free from interference…

- in audit scope determination,
- in PV audits performance, and
- in audit result communication.

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How is an Inspection different from an Audit?

Audit

Performed by Sponsor/CRO

Non-compliance repercussions not severe

Vested interest in ensuring PV process success

Inspection

Performed by Regulatory agency

Non-compliance repercussions can be severe

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What is an Inspection?

The act **by a regulatory authority(ies)** of conducting an official review of **documents, facilities, records, and any other resources** that are deemed by the authority(ies) to be related to pharmacovigilance and drug safety.

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Objectives of Inspections

To determine that the MAH has personnel, systems and facilities in place to meet their PV obligations

To ensure compliance with co requirements

Most Importantly:
To ensure Patient Safety

To be used as a basis for enforcement action

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Types of Inspections

System and product-related inspections	Focused on product-related PV issues, rather than a general system review
Routine and "for cause" inspections	No specific trigger may initiate inspections
	A risk-based approach to optimize may be implemented
Pre-authorisation inspections	Inspections performed before a marketing authorisation is granted.
	Conducted with the intent of examining existing or proposed PV system
Post-authorisation inspections	To examine whether the MAH complies with PV obligations.
Re-inspections	May be prioritized based on risk factors
Remote inspections	Performed remotely at premises of the MAH or firms employed by the MAH. Use internet or telephone.

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Some Common Triggers for 'For-cause' Inspection

- Change in risk-benefit balance
- Delays or failure to identify or communicate a risk or a change in the risk-benefit balance
- Communication of information on PV concerns to general public without informing NRA
- Issues with expedited and periodic reporting: delays or omissions, poor quality reports, inconsistencies in data
- Poor quality data or failure to provide the requested information or data within the deadline specified by NRA
- concerns about the status or fulfilment of risk management plan (RMP) commitments
- other sources of information or complaints.

Majority of inspections will be announced

Can be unannounced or at short notice

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Sites for Pharmacovigilance inspection

Central hub for global Pharmacovigilance

Company Affiliates (i.e., Country Office)

Marketing Partners

Contract Research Organizations

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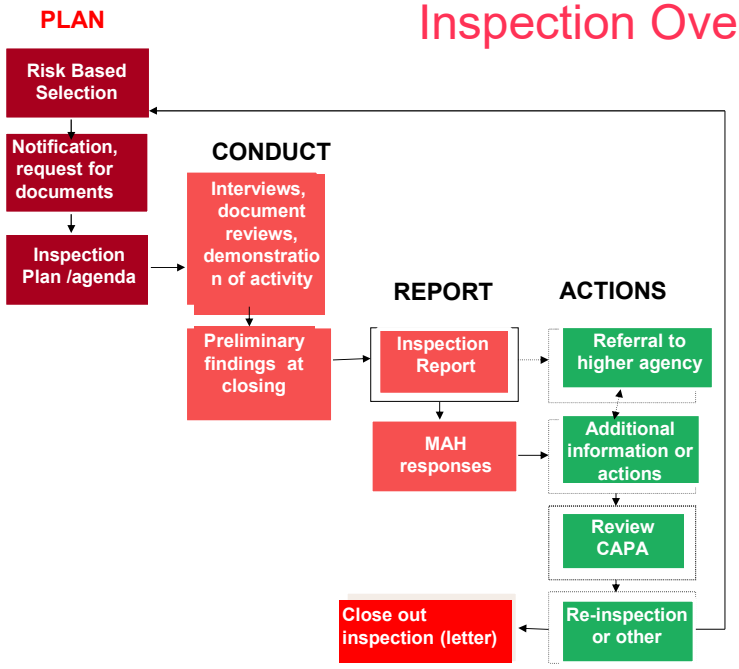
Inspection Overview



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Conduct of Audit/Inspection

Opening meeting

Introductions, review audit/inspection plan

Audit/Inspection

Interviews

Document review

Demonstration of process

Database searches

Tour of Pharmacovigilance, Medical Information, archives and computer server rooms

Closing meeting

Findings communicated

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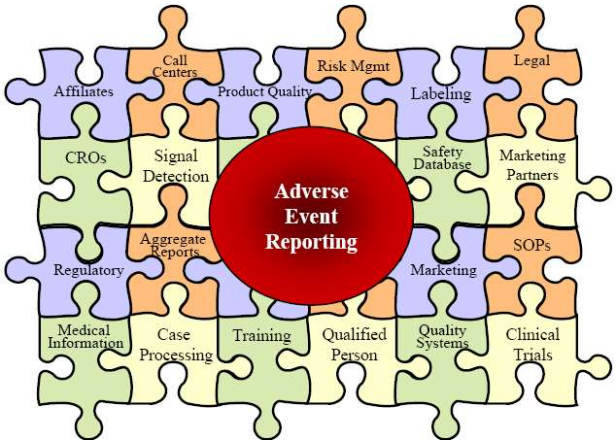
Scope of Pharmacovigilance Inspection

All pharmacovigilance processes and activities and related documents!



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When to prepare for an inspection?

Everyday!

- Have a positive outlook
- Know your role and job responsibilities
- Know your Standard Operating Procedures and Standard Working Practices…and follow them
- Ensure that your training records are up to date
- Work areas should be uncluttered

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PREPARATION: Once Announced

Functional Leaders

- **Discuss** potential for inspection and what to expect
- **Identify key people**, roles and responsibilities
- **Delegate** pre-inspection assignments
- **Ensure documentation** is available, accurate and complete
- **Review** past corrective action plans

All Leaders/Individual Contributors

- Review all essential documents/internal SOPs
- Clear all areas of documents
- Ensure personnel training is current

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During the Inspection – Best Practices

Relax, don't panic!

Be polite, cooperative, confident, and professional

Escort the inspector at all times

Keep track of all questions and requests (daily notes)

Ask for clarification to questions and /or requests you do not understand

Maintain a log of all documents requested

Clarify misunderstandings in real-time as they occur

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Sample Questions - Interview

All Personnel	Managers	Senior Management
• What do you do? • What are your responsibilities? • How were you trained? • Can you demonstrate what you do?	• How are staff trained? • How are staff competencies assessed?	• How many staff and where based? • Are all computer systems within the office fully validated?

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‘GOOD’ Interviewing

Do	Take a deep breath
	Project confidence and professionalism with your body language and voice tone
	Listen carefully to the Inspector’s questions
	Pause and formulate a proper response
	Request clarification to questions not understood
	Answer only what was asked
	Provide a clear, concise, and honest answer
	Only answer questions within your job responsibilities

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‘GOOD’ Interviewing

Don’t	Volunteer information
	Guess the answer or speculate
	Provide false information
	Make decisions for Management.
	Provide excuses or shift blame.
	Answer questions which are outside your responsibility / expertise
	Answer hypothetical questions
	Make any assumptions on the question or request
	Have “filler” conversations with inspectors – treat all conversations with the inspector as “on the record”
	Say that something is impossible or would never happen

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After the Inspection – Best Practices

Exit Meeting

- Ensure appropriate company personnel are present for Exit Meeting
- Clarify misunderstandings
- Confirm reporting and response procedures
- Communicate corrective actions implemented during the inspection

Don't wait for an inspection report to begin addressing identified non-compliances

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Inspection Success Factors

- Understanding of inspectors' objectives
- Management and staff support
- Internal audit program
- SOP & system to manage inspection
- Successful communications

Sustained Inspection readiness

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Common findings: System Failures

Multiple serious deficiencies in all areas of pharmacovigilance system taken together" or no system in place (less common)

Example

No global PV system due to:

- inadequate safety data exchange with affiliates/subsidiaries
- no timescales or formal arrangements for the transfer of ICSRs or other safety information.

Resulting in…

either lack of or late expedited reporting of ICSRs and PSURs containing incomplete safety data.

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Common findings: Qualified Person for Pharmacovigilance (QPPV)

- No QPPV or interim measures (change of QPPV, back-up procedures for absence etc.)
- Inadequate oversight of the PV system
- Lack of training and/or experience
- Roles and responsibilities not formally defined
- Inadequate access to medically qualified personnel

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Common findings: Processing of ICSRs

- Lack of reconciliation
  - Internal (medical information, product quality)
  - External (distributors, manufacturers, licensing partners)
- Lack of follow up
- Late reporting of cases requiring expedited reporting
- Lack of QC check (Data entry, expedited reporting decision)

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Common findings: Literature Searching

Inadequacies in the construction of, or process used for, literature searching

- sources used
- adequacy of scope of search with respect to search objective
- local literature scanning
- language restrictions
- lack of QC

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Common findings: Quality Management System

Procedural documentation

None exist / insufficiently detailed

Do not reflect practice

Training not done or even lack of awareness by staff of existence of procedure

Training

Inadequate or absent

Lack of refresher training

Restricted to PV department

Quality Assurance Auditing

Lack of PV audits (conducted and future plans)

Extent of audits (affiliates, contractors)

Record retention

No definition of how long documents (and which documents) should be stored

No system to ensure documentation remains in a readable and understandable state.

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Common findings: PSURs

Production – No procedure, not in desired format, not a consistent standard

Lack of Quality control

Incomplete – missing cases, no summary tabulation, does not address Competent Authority requests

Submissions – No mechanism to track, late submissions, no submission

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Common findings: Contracts and agreements

Lack of contracts with third parties, or contracts still in draft

Insufficiently detailed

- Responsibilities of each party
- Exchange of Adverse Reactions (and other special situation cases) and product complaints
- Timelines
- Reconciliation…

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Common findings: Others

IT systems and Business Continuity

- Validation of IT system inadequate
- Backup procedures missing or inadequate
- Insufficient access control
- Inadequate disaster recovery / business continuity plans

Medical Information

- Out of hours service inadequate / not tested

Pharmacovigilance System Master File

- Inconsistent with current system in place

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Audit/Inspection Outcome Action and their Follow-up

Actions to be taken can be

- immediate,
- prompt,
- ones within a reasonable timeframe,
- requires to be addressed, or communicated urgently in an expedited manner

Actions should include:

- root cause analysis
- impact analysis of identified risk and
- a corrective and preventive action (CAPA) plan

CAPAs addressing the critical and major issues should be prioritized

Evidence of actions implementation and completion should be recorded to document that issues raised have been addressed

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Responding to the findings in an Audit/Inspection report

Understand	Assess	Prepare	Develop
Understand the observation and seek clarification as needed	Assess root cause / underlying issue	Prepare Corrective and Preventative Action (CAPA) • Formulate a coordinated response with input from relevant parties • Consider impact of response on global or local operations	Develop CAPAs that are SMART • **S**pecific • **M**easurable • **A**chievable • **R**ealistic • **T**ime Driven

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SMART Responses (example)

Finding

The Company has not been actively following up spontaneous reports of patients who have become pregnant while taking one of the Company's products.

Response

SOP XXXXX1 (Follow-up procedures for spontaneous reports) will be **updated by 30th Oct 2021** to **include clear follow-up procedures** for any reports of potential pregnancies received by company personnel. All appropriate **staff will be re-trained** on the updated version of this SOP prior to its implementation.

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Non-SMART Response (example)

Finding

There is no formal written procedure in place to cover the PSUR production process.

Response

An SOP will be implemented.

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Consequences of Non-compliance

Education and Facilitation

MAH may be informed of non-compliance and advised on how this can be remedied.

Meeting with senior MAH representatives to discuss issues and consequence of non-compliance

Re-inspection

Non-compliant MAH is inspected to determine the extent of non-compliance and re-inspected to ensure compliance is achieved

Warning

Authority may issue a formal warning reminding MAH of pharmacovigilance obligations

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Consequences of Non-compliance

Naming non-compliant MAH

Authority will consider a policy of making public a list of MAH found to be seriously non-compliant

Marketing Authorization related actions

Urgent Safety Restriction

Variation of the MA

Suspension of MA

Revocation of the MA

Criminal prosecution

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Take Home Points

- Ensure staff is qualified and trained
- Have quality systems in place to ensure data / process quality
- Keep active relationships in place with other relevant functional areas (e.g., Manufacturing, Quality Assurance, Clinical/Medical, Marketing, Sales, etc.)
- Internal pharmacovigilance audits are very important
- Do everything in anticipation and preparation for an inspection
- Documentation is essential

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Thank You

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