Managing Pharmacovigilance Audits and Inspections

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16th June 2021

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
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
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

Strategic Level Audit Planning: Factors 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
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)

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
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

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.
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.

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
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.

Objectives of Inspections

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

To ensure compliance with company procedures and local/global regulatory requirements

Most Importantly:

To ensure Patient Safety

To be used as a basis for enforcement action
### Types of Inspections

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

Central hub for global Pharmacovigilance

Company Affiliates (i.e., Country Office)

Marketing Partners

Contract Research Organizations
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

Scope of Pharmacovigilance Inspection

All pharmacovigilance processes and activities and related documents!
When to prepare for an inspection?

- 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

Everyday!

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
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

Sample Questions - Interview

All Personnel
- What do you do?
- What are your responsibilities?
- How were you trained?
- Can you demonstrate what you do?

Managers
- How are staff trained?
- How are staff competencies assessed?

Senior Management
- How many staff and where based?
- Are all computer systems within the office fully validated?
‘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

‘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
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

Inspection Success Factors

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

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
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)

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
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.

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
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...

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
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

Responding to the findings in an Audit/Inspection report

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<tr>
<th>Understand</th>
<th>Assess</th>
<th>Prepare</th>
<th>Develop</th>
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<tbody>
<tr>
<td>Understand the observation and seek clarification as needed</td>
<td>Assess root cause / underlying issue</td>
<td>Prepare Corrective and Preventative Action (CAPA)</td>
<td>Develop CAPAs that are SMART</td>
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<td></td>
<td></td>
<td>• Formulate a coordinated response with input from relevant parties • Consider impact of response on global or local operations</td>
<td>• Specific • Measurable • Achievable • Realistic • Time Driven</td>
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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.

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.
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

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
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

Thank You