Module 12: Pharmacovigilance (PV) Audits & INSPECTIONS

Agenda

- Internal PV Audits – Types & Basic Principles
- Audit Process in details
- PV Inspections
- During the Audit/ Inspection
- General findings/ trends
- Corrective actions and Preventive Actions (CAPAs) and Responses

What is an Audit?

Audit: A systematic and independent examination of activities to determine whether the evaluated activities were performed according to defined requirements.*

Inspection: The act by a **regulatory authority** of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority to be related to the regulated activities.

Key Words in Definition

- Systematic : organized, methodical, planned
- Independent : unbiased, no conflict of interest, objective
- Examination : assessment, evaluation, investigation
- Defined requirements : audit criteria, regulations, procedures

*This definition compiled from an extraction of ICH and ISO definitions.

Why Perform an Audit?

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

–To ensure company regulatory obligations / commitments are met

–Evolving regulatory requirements

–Inspection readiness: increasing Regulatory Inspections – Internal detection of risk is essential

–To identify process / quality improvements

Types of PV System Audits

- Global PV systems/processes
- Company Affiliates (i.e., Country Office, Local Operating Company, Marketing Company)
- Marketing (Licensing) Partners
- Vendor Audits

Global PV System Audits

- Focus on central Pharmacovigilance processes
- Assess compliance with company procedures and global Pharmacovigilance regulations
- Sample of products across therapeutic areas and a defined timeframe (vehicle to assess the system / process)

Affiliate Country Office Audits

Primary focus on local PV responsibilities

- Assess compliance with local and global company procedures and regulatory requirements (as applicable)
- Evaluate the flow of safety information (from all applicable sources) from initial receipt to reporting to external parties
- Involves many functional groups that impact the Pharmacovigilance system
  - -Pharmacovigilance
  - -Regulatory Affairs
  - -Medical/Clinical
  - -Marketing
  - -Sales
  - -Product Quality
  - -Information Technology
  - -Medical Information
- Not just an audit of local affiliate but also of global processes to support local affiliates

Affiliate Country Office Audits

Topics most often covered within scope:

- Adverse event (AE) collection and processing
- Expedited reporting to regulatory authorities
- SUSAR distribution
- Product Quality Complaint handling
- Safety surveillance
- Local quality systems (including compliance monitoring)
- Regulatory functions (e.g., Aggregate reports submission, Labeling, regulatory Authority query management, etc.)

Affiliate Country Office Audits (Contd.)

Topics most often covered within scope:

- –Contracts and Agreements (Marketing Partners, CROs, etc.)
- –Medical Information
- –Promotional Material
- –Standard Operating Procedures (SOPs)
- –Training
- –Document Retention / Archive
- –Electronic systems used to support the Pharmacovigilance system
- –Business Continuity / Disaster Recovery

Pharmacovigilance Partner Audits

- Marketing partner [Licensing partner] Audits
- Includes in-licensed and out-licensed product agreements
- Focus on compliance with Marketing Partner agreement
  - –Ensure PV roles and responsibilities are defined and performed
  - –Ensure appropriate exchange of safety information
- Assess compliance with local and global company procedures and regulatory requirements (as applicable)
- Performed independently by company, or jointly or by Consultant
- Due-Diligence assessments - Licensing and Acquisition

PV System Audit Program Fundamentals

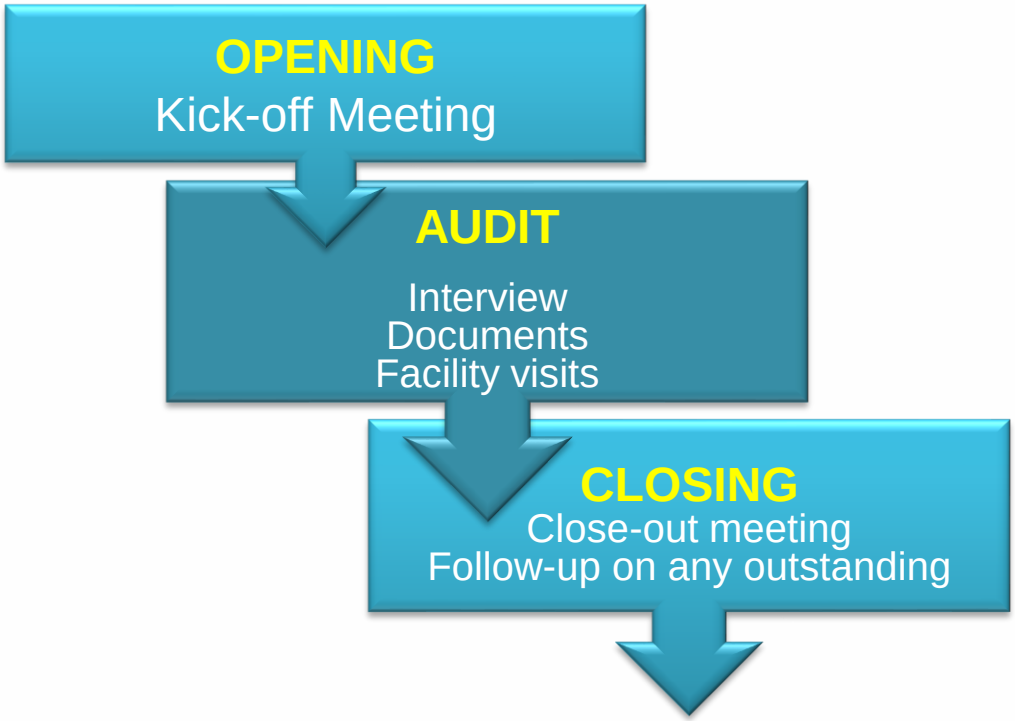
- Risk Management / Audit Scheduling
- Identify universe of company PV systems, affiliates, and marketing partners
- Identify critical risk factors / indicators* to measure each entity in the universe
  - ✓ Volume of AE Cases
  - ✓ Clinical Trial (CT) Activity
  - ✓ Number of External Contracts / Agreements
  - ✓ Previous Audit / Inspection History
  - ✓ Compliance data

PV System Audit Program Fundamentals (Contd.)

- Receive input from key stakeholders on proposed schedule e.g.,
  - Head of Safety,
  - QPPV,
  - Regional Safety Representatives, etc.
- Communicate forward-looking schedule to global audience

- Risk factors / indicators may differ for Global PV Systems, Affiliates and Marketing Partners

AUDIT SEQUNCE



Audit Program – Process Flow

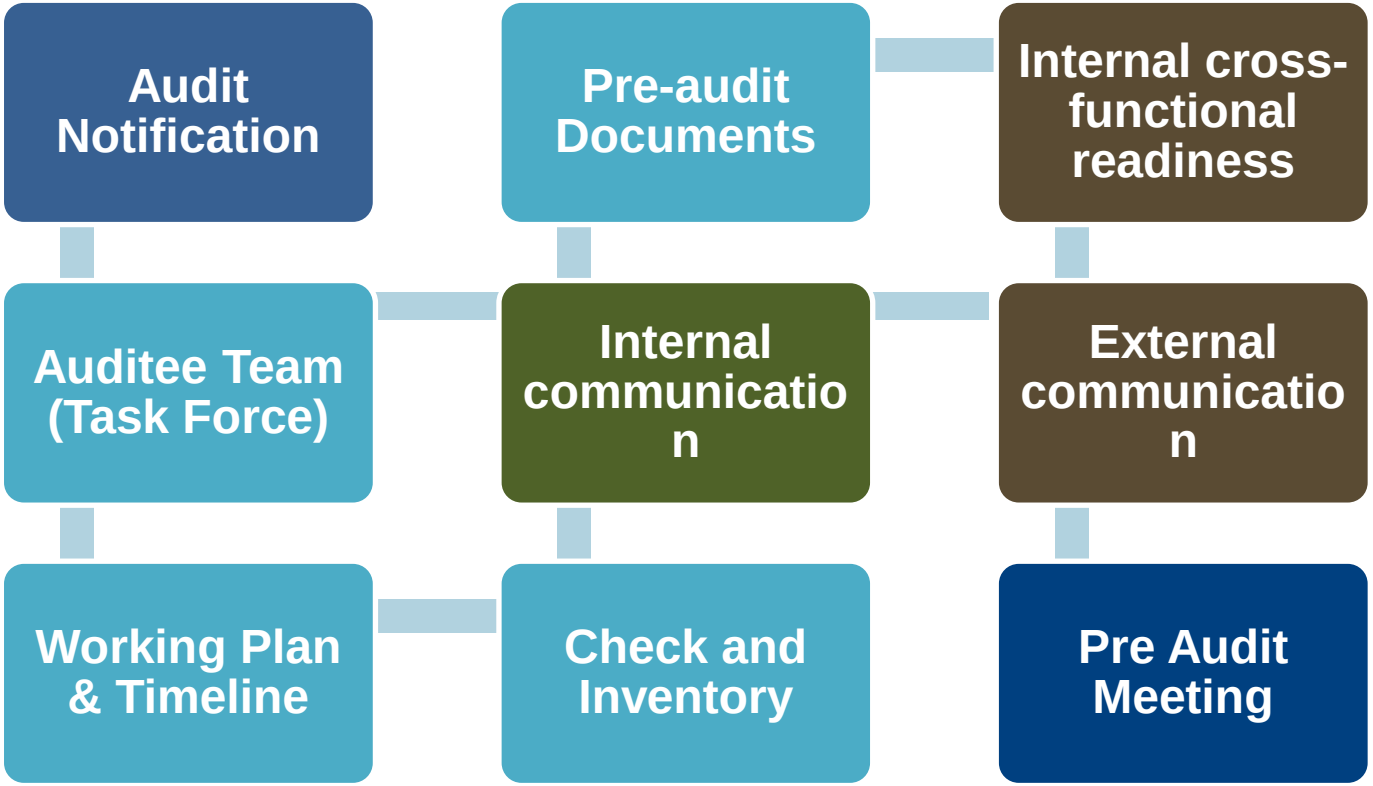
Timeframes for each of these audit phases may vary based on company procedures, type of audit, and defined scope.

Audit Planning and Preparation

- Pre-audit meetings to understand organization and scope of processes
- Identification of system owners
- Development and agreement of an audit plan defining audit objectives, scope and roles/responsibilities
- Pre-audit document requests to provide framework for regulatory environment and audit conduct strategy (e.g., sampling strategy, interviews, etc.)
- Development and agreement of audit agenda defining topics and personnel involved along with proposed time*

*Agendas generally require flexibility

Audit Readiness



Involvement of other Functions/Depts

- RMP responsible
- Quality Assurance
- Regulatory Affairs
- Clinical Research
- Medical Information
- Medical Affairs

Audit Conduct

- Opening / Introductory Meeting to “kick off” the audit
- Interviews with relevant personnel
- Document reviews
- Demonstration of activities (e.g., processing of an adverse event case)
- Tour of facilities (e.g., work areas, file storage and archiving)
- Closing / Exit meeting to discuss preliminary results
- Follow-up on outstanding questions / requests

Subject to be Audited

- AE Reports
- PV Resources
- Training
- SOP & Procedures
- Contract & Agreement
- RMP
- Business Continuity Plan
- Document Retention/Archived

Subject to be Audited: Source of AE Reports

* Counterfeit, Diversion, Tampering

Subject to be Audited: AE Case Processing

Spontaneous AE	Communication Devices	Reconciliation
Serious AE	Out of Office Hour/Holiday	Marketing Program
Pregnancy	Delegation	Correspondences with H.Authority
SAE from Observational Study	Follow-Up	Medical Devices

Subject to be Audited: PV ~~Resources~~

- QPPV: dedicated, part of other roles (?)
- Organization Chart
- CV and Job Description
- Delegation/Back-up

Subject to be Audited: TRAINING

PV Personnel	Employee	Third Parties/Partners
• Internal SOP & Procedures • Global Regulations • Local Regulations • Good Documentation • Supporting Tools • GCP	• AE Reporting • RMP • RMP for specific Product • Patient Program	• AE Reporting • RMP

TRAINING PLAN

TRAINING RECORDS

Subject to be Audited:
PV Contractual Agreement

- Local PV Agreement
  - Template (separate, clausal)
  - Current version
  - List of Agreement (dated)
  - Local Review Process

Subject to be Audited:
Risk Management Plan

- RMP Trainings to employee & partners
- Specific Brand RMP training for Sales/Marketing & partners
- Documentation of Implementation
- List of current RMP (date)

Audit Reporting

- **Audit report issued within defined timelines**
  - –Executive Summary
  - –Description of 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
    - »Judgment / Rating (e.g., Critical, Major, Minor, etc.) based on company … . rating scale
  - –Process / Quality Improvement Opportunities

Corrective and Preventative Action (CAPA)

- Understand the observation and seek clarification as needed
- Assess root cause / underlying issue
- Develop CAPAs that are:
  - **Specific:** Action resolves the issue and aims to prevent reoccurrence
  - **Achievable:** Action that is realistic and in accordance with regulations
  - **Time Driven:** Identify realistic timeframe for completion (based on risk)
  - **Accountable:** Action has clear accountability defined
- CAPA development is one of the most important aspects of successful audits

Audit Follow-up and Closure

- Periodic follow-up on open CAPAs until closure (may be risk based)
- Confirmation or verification of completion may be required (may be risk based)
- Audit closure when applicable CAPAs have been completed
- Utilize audit experience to build a culture of continuous improvement and audit / inspection readiness

Inspection

Inspection Vs Audit

AUDIT

- Purpose : assess GxP compliance, reliability of data, works toward process improvement, preparation for regulatory inspection
- Sanctions : recommendations made to global/ subsidiaries/ partners
- Style : *co-operative*

INSPECTION

- Purpose : to verify, on behalf of the community that the MAH satisfies the regulatory requirements, reliability of data and ensure rights and welfare of patients are protected
- Sanctions : many and powerful
- Style : always very formal and structured atmosphere varies from aggressive by some inspectors to more open by others

Why PV Inspections

- To determine that the Marketing authorization Holder (MAH) has resources (**people, systems** and **facilities)** in place to meet their PV obligations
- To identify, record and address **non-compliance** which may pose a risk to public health
- To use the inspection results as a basis for **enforcement action**, where considered necessary

Global PV Inspection Trends

Past	Present
• Site based • Product safety data specific • Independence between Regulatory Authorities globally • Limited frequency • Mostly FDA Inspections	• Systems based with safety and /or compliance data as a potential trigger • Focused on PV system –across sites / operations / products • Scope includes linkages and relationships across the company to perform Pharmacovigilance responsibilities • Increased inspection activity globally (FDA, MHRA, EMEA, etc.) • Increased collaboration across regulatory authorities globally

Types of Inspections

- System and product related inspection.
- Routine and “for cause” inspections
- Pre-authorization Inspections
- Post-authorization inspections
- Announced and unannounced inspections
- Re- inspections
- Remote inspections

How Inspections are planned

- Inspection related
  - Compliance history/ re-inspection
- Product related
  - PASS, RMP
- MAH related
  - No previous inspection, merger, acquisition
- PV system related
  - Change of QPPV, out sourcing, new safety database

Most inspectorates apply a risk assessment model to target limited resources at the highest risk areas

Are you Inspection Ready?

- Do you have an inspection plan and contact list (and routinely test it)?
- Do you have procedures in place?
  - –Are they current?
  - –Are they retrievable?
- Do you report, process, and submit adverse events (from all potential sources) within required timelines?
- Do you comply with company procedures and applicable regulations?
- Are your staff qualified and trained?
- Do you have quality systems in place to ensure data / process quality?
- Do you know where your documentation is maintained?
- Are active relationships in place with other relevant functional areas (e.g., Manufacturing, Clinical/Medical, Marketing, Sales, etc.)?

Inspection Logistics

- Inspection room
- Inspection Coordinators (Company QA department)
- Scribe
- Interviewee
- QA representative (s)
- Relevant representatives from different functional areas
- Runner(s)/ Next interviewee
- Establish Document Flow/Use of Common Email folders/ Common drives
- Inspection area should be in quiet area –far from all operational activities

Document request

- CVs, job descriptions and training records for interviewees
- Organization charts/organograms (with names and job titles)
- Procedural documents (e.g. SOPs, working instructions etc)
- Individual adverse reaction cases files and CIOMS reports
- PSURs, DSURs, PBRER
- Signal detection outputs
- Contracts and agreements with third parties
- Risk Management Plans
- Meeting minutes
- Written communications to and from the Competent Authorities
- Product information, including SmPCs and PILs

During the Inspection

Interview process - Technique

- Inspectors will put you at ease –Ask about your background etc.
- Ask about role in the company
- You daily activities.
- The training you received to perform your role and responsibilities.

- Ask specific questions, but open

- Request evidence to support statements.
  - Inspectors do not intend to trick you but be aware of: Long silences. *You are not required to fill them*.
  - Inappropriate questioning (should be picked up by QA)
  - Inappropriate challenges
  - An invitation to ‘spill the beans’

After the Inspection

- 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
- The inspection does not end when the inspectors leave the building!
- The inspectors may make additional requests for information following the inspection.

Grading of inspection findings

- **Critical:** a deficiency in PV systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

- **Major:** a deficiency in PV systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

- **Other:** a deficiency in PV systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Regulatory Actions and Sanctions -1

- Education and facilitation
- Provision of information to other competent authorities
- Warning letter, non-compliance statement
- CAs may consider making public a list of MAH seriously or persistently non-compliant.
- Actions against a marketing authorization(s) or authorization application(s) e.g.
  - Urgent Safety Restriction;
  - Variation of the marketing authorization
  - Suspension or revocation of the marketing authorization;
  - Delays in approvals of new marketing authorization applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorizations;
  - Requests for pre-authorisation inspections

Regulatory Actions and Sanctions -2

- Inspection, Re-inspection
- Product recalls e.g. where important safety warnings have been omitted from product information;
- Amendments or suspension of clinical trials due to product-specific safety issues
- Administrative penalties, usually fixed fines or based on company profits or levied on a daily basis
- Referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

Thank you