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Developing Countries Vaccine Manufacturers Network

**Vaccine Safety Monitoring**
**DCVMN Regional Training Workshop**
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# Pharmacovigilance Systems and their Quality Systems:

## Audits and Inspections

## Contractual Agreements

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# What is a Pharmacovigilance Audit?

**General (Dictionary of Pharmacovigilance):**

"A systematic and independent process by which activities and documentation can be assessed and evaluated against agreed procedures to establish levels of compliance, competence, effectiveness, and probity ..."

**EU GVP Definition:**

"A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011 (3.1)2)."

*Benchmarking, reviews of qualifications, risk assessment questionnaires, surveys or other activities in which evidence of fulfilment of pharmacovigilance requirements is not independently obtained and evaluated, would not be regarded as an audit.)*

# Purpose, Objectives and Types of Audits

- To ensure compliance with company procedures and local / global regulatory requirements:
  - Audits are mandatory (EU) or expected by Regulators
- To ensure company regulatory obligations / commitments are met
- To prepare for regulatory inspections
- To detect internally system gaps
- To identify process / quality improvements
- To ascertain that pharmacovigilance staff / company staff have adequate / appropriate training
- To assess delegation of legal responsibilities to vendors and contractural obligations

- Global Pharmacovigilance system / process audits
- Company Affiliates (i.e., Country Offices, Local Operating Companies, Marketing Company)
- Licensing Partners

Audits provide Company-wide awareness of Pharmacovigilance

# Pharmacovigilance System Audits /1

- Systems approach focused on business processes:
  - Case collection and processing (AEFI from post-marketing / SAEs from clinical trials)
    - Overall case processing
    - AEFI assessment and triage
    - AEFI coding and code review
    - Medical review
    - Case narrative
  - Regulatory reporting / Regulatory functions
    - Expedited reporting of individual case safety reports (7-day / 15-day reports)
    - Periodic reporting (DSURs, PSURs)
    - Labeling
    - Regulatory Authority query management
  - Signal detection process / Safety surveillance
  - Risk management process
  - Literature search
  - Medical Information
  - Product Quality complaint handling / AEFI reconciliation

# Pharmacovigilance System Audits /2

- Evaluate the flow of safety information from all applicable sources from initial receipt to reporting to external partners
- Safety database and electronic systems to support pharmacovigilance
- Skills and resource level
- Structure of the company's pharmacovigilance organization
- PV Quality Management
  - Quality assurance and quality control processes
  - Performance monitoring and metrics
  - SOP
  - Training
  - Document retention / Archiving
- Business continuity / Disaster recovery
- Assess compliance with company procedures and global Pharmacovigilance regulations (e.g., ICH, EMA, FDA, national regulations)
- Assess compliance with Marketing Partner agreements
  - Ensure pharmacovigilance roles and responsibilities are defined and performed
  - Ensure appropriate exchange of safety information

# Company sources of information
## to be examined - Examples

- Process / workflow diagrams
- Organization charts
- Safety Data Exchange Agreements
- Current Safety SOPs
- Sampling of cases
- Safety specifications and Risk Management Plans
- Signal tracking list
- List of Product complaints with AEFI reconciliation

# Audit Procedures

- Preparation
  - Audit agenda
  - Identify and confirm all roles and responsibilities of staff involved
  - Obtain and review the documents requested in advance by the auditors
  - Prepare audit back-office
  - Compile questions for relevant auditees
- Opening Meeting – Meeting to kick-off the audit
  - Explain the audit and QA plan / scope of the audit
  - Confirm date / time still ok
  - Explain the course of the audit
  - Request further documents that could not be requested earlier
- Audit conduct
  - Interviews with the responsible staff on the respective processes / SOPS / workflows
  - Document reviews
  - Demonstration of activities
  - Physically walk through the safety processing system (e.g., work area, file storage, archiving)
- Closing / Exit meeting
  - Discussion of preliminary results
- Audit Report
- Follow-up – CAPAs

# 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
  - Judgement / Rating – e.g. Critical, Major, Minor based on Company Rating Scale
  - Process / Quality improvement opportunities

# Rating of Audit / Inspection Findings

In general, 3 rating categories of findings:

- Critical
- Major
- Minor (Other)

Definitions (wording may vary slightly between different companies / Authorities):

- Critical: Deficiency in pharmacovigilance 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: Deficiency in pharmacovigilance 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.

- Minor: Deficiency in pharmacovigilance system, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

# CAPAs
## Corrective and Preventive Actions

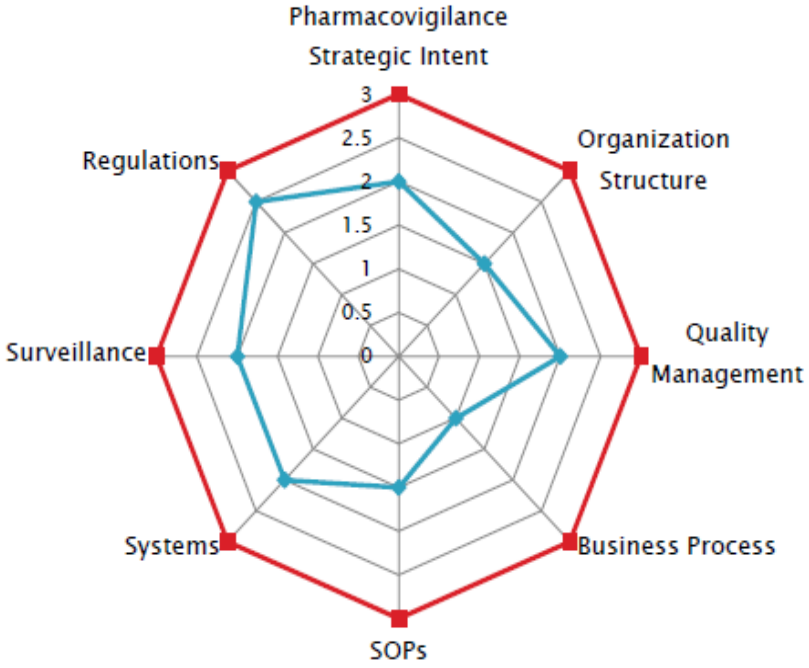
CAPA development is one of the most important aspect of a successful audit.

- Understand the observation and seek clarification
- 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 the Regulati0ons
  - Time driven: Identify realistic timeframe for completion (based on the risk)
  - Accountable: Action has clear accountability defined

# Audit Follow-up / Closure

- Periodic follow-up on open CAPAs until closure
- Confirmation or verification of completion
- Audit closure when applicable CAPAs have been completed
- Utilize audit experience to build a structure of continuous improvement and audit / inspection readiness.

## Audits support the company to establish the Pharmacovigilance Risk Profile




Red: Best Practices

Blue: Audit Results

# What is a Pharmacovigilance Inspection?

**Pharmacovigilance System Inspections** conducted by Regulatory Authorities are designed to review the procedures, systems, personnel, and facilities in place to determine their compliance with regulatory pharmacovigilance obligations.

**Product-related pharmacovigilance Inspections** conducted by Regulatory Authorities focus on product-related pharmacovigilance issues, incl. product-specific activities and documentation.

Pharmacovigilance data / safety data and respective processes are also reviewed as part of **GMP and GCP inspections**.

# Potential Triggers for Inspection

- Routine Inspection:
  - No specific safety trigger
  - Within a risk-based National Agency's Inspection Program
  - Pre-authorization inspections: Regulators may assess the Pharmacovigilance System at introduction of a new product / WHO prequalification

- For Cause Inspection:
  - Late submission / poor quality of 7- / 15-day reports
  - Late submission / poor quality of PSURs / DSURs
  - Inability to deliver PSURs / DSURs
  - Inconsistencies between different PSURs
  - Inconsistencies between PSURs and Clinical Study Reports / DSURs
  - Poor follow-up of initial AEFIs
  - Quality issues giving rise to safety issues
  - Concerns about fulfilment of commitments (e.g., RMPs, Safety Reports)
  - Poor quality or inadequate fulfilment of requests from Regulatory Agencies

# Pharmacovigilance Inspection topics (MHRA)

| Topic Area | Sub-topic of reported findings |
|---|---|
| **Collection and collation of adverse reactions** | • Spontaneous sources of safety data, e.g., medical information, product quality complaints<br>• Literature searching<br>• Solicited sources of safety data |
| **Management of adverse reactions** | • Case processing: data entry, coding, assessment, follow-up and reporting<br>• Data management, including migration of safety data |
| **Risk management** | • Management of additional PV activities as part of RMP<br>• Maintenance of reference safety information<br>• Additional risk minimization activities as part of RMP<br>• Safety communication<br>• RMP maintenance |
| **Quality management system** | • Procedures, record management, training, PV contracts<br>• Audit and deviation management, incl. CAPA management<br>• PV system oversight and governance, incl. Performance monitoring and role of QPPV<br>• Information technology systems and applications |
| **Provision of infpormation for supervisiion by national authority and inspection** | • Inspection readiness<br>• Management of the description of the pharmacovigilance system<br>• Submission of information to national authorities |
| **Clinical trials pharmacovigilance** | • Clinical trials pharmacovigilance (e.g., maintenance of RSI for clinical trials, SUSAR reporting |

# Inspection Procedure

- Inspection announcement / Unannounced Inspection
  - Regulators have the right to perform a Pharmacovigilance Inspection at any time
- Preparing for Inspection
  - Preparation of an Inspection Plan
  - Inspection team and inspection dates
  - Specific documents, tools etc. to be reviewed (similar to documents provided at audits)
- Arrangements with Inspectors
- Conducting on-site inspection, typically 1-4 days depending on Inspector's Agenda – similar to Audits (e.g., Mock-Inspection Audits)
  - Opening Meeting
  - Collecting and verifying information
  - Closing Meeting – similar to Audit Closing Meeting
- Inspection Reporting
  - Inspection-related data
  - Introduction to and summary of inspection activities
  - Inspection observations and findings
  - List of deficiencies during inspection
  - Name and signature of the Inspector
- Inspection Follow-up
  - Follow-up until a CAPA plan that appropriately addresses the non-compliance is completed

# Traditional Inspector's Questions

- What do you do?
- Describe your role & responsibilities?
- How do you know how to do your job?
- What procedures / legislation do you follow?
- Can you show me what you do?
- How are you qualified to conduct your current role?

# Interview Preparation

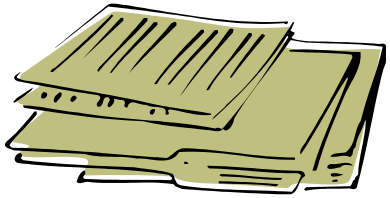
- Try to identify potential areas of concern before the inspection (deviations/ issues).
- Familiarize with key issues, e.g. management of non-compliance
- Ensure familiarity with previous inspection findings, resulting actions, changes to process, etc.
- Show improvements and plans.
- Do not offer adverse information unless requested to do so.
- Aim to be consistent with representatives from the same department.

# What do I need to be able to Do / Provide during the Inspection?

- Describe / explain your role and the job that you do
  - Ensure you know the processes
- Be able to describe and identify SOPs & written procedures governing your work
- Describe what you do to manage and control the interfaces (handovers) with your customers / client groups
- Provide documentation of your actions and activities, if requested

Be prepared……..

Know what you do
Say what you do
Do what you say
Prove what you did



# Common Inspection findings

- Failure to submit or late expedited and periodic reports
- Inaccurate or incomplete reports to Authority questions or requests
- Failure to do follow-up for serious and unexpected AEFIs
- Lack of or inadequately written SOPs
- Failure to follow the company's own SOPs
- Database issues, incl. inadequate validation and security
- Deficiencies of QPPV (if applicable)
- Technical issues: incorrectly formatted submissions and reports
- Poor quality of PSURs or ICSRs
- Safety signals missed, ignored, or poorly assessed
- No or poor-quality risk management processes
- No or poor-quality pharmacovigilance management system
- Labeling problems (e.g., CCSI, SPC, package insert, patient information)
- Lack or inadequate metrics and performance measures
- Problems and CAPAs from previous inspections not corrected and / or promises not kept

# Processes of concern /1

- Ongoing safety evaluation / Signal management
  - Detection and evaluation
  - Identification of change to benefit / risk
  - Notification to authorities
  - Completion of commitments
- Risk Management System and Risk Minimization Commitments
  - RMP in line with known safety concerns and the current risk management system for defined products
  - Adherence to RMP commitments
  - Regulatory safety requests and commitments
    - Awareness of requests
    - Tracking requests
    - Timetable for response
    - Content of response
    - Fulfilling commitments

# Processes of concern /2

- Registration activities
  - Awareness of applications for marketing authorization
- Third party obligations
  - Identification of licensing partners
  - Adequacy of existing pharmacovigilance agreements
  - Procedures covering new licensing arrangements
- Regulatory intelligence
  - Awareness of changes to regulation
- Safety database and associated systems
- Activities at a global HQ and worldwide affiliate level – for the PV system to work
- Activities at a national affiliate level in the EU/EEA and non-EU countries – for the PV system to work

# Inspection - Points to consider

- Good working Inspection Team and good preparation is key to successful inspection
- Pharmacovigilance is not only a task of the Pharmacovigilance department – demonstrate that Communications and Interfaces between Departments work
- Interviewees should be:
  - experienced staff
  - staff prepared for the inspection
  - staff directly involved in the process inspected (no new staff members)
  - ideally present in person (avoid TCs if possible)

After Inspection, work is not over – ensure CAPAs are implemented. The authority follows up !

# Sanctions of Non-Compliance / Penalties

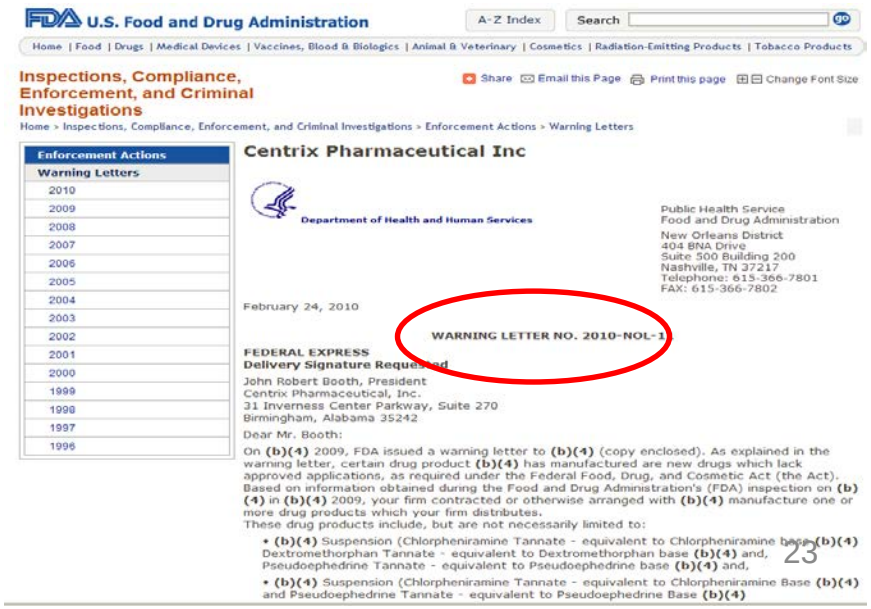
EU: Possible penalties for non-compliance with PV requirements (CPMP/PhVWP/1618/01):

- criminal sanctions (personal fines, imprisonment)
- civil liability (claims for negligence)
- regulatory (revocation of authorization, regulatory inspection, **loss of credibility with authorities**

US: Variety of sanctions for non-compliance (Guidance for FDA Field Staff):

- FDA 483: Report of deficiencies requiring a response and action
- warning letter to CEO, published on FDA website
- Cessation of sales, termination of NDA
- Criminal prosecution

National Regulatory Agencies: ……



# Business Partners and Exchange of Safety Data

Various types of business partners / third parties that may receive safety information :

- Service Providers (CROs) for pharmacovigilance activities (outsourcing)
- Third-party distributors
- Third-party manufacturers
- Co-marketing, co-licensing and co-promotion of vaccine
- Co-development of vaccine

Preparation of a business agreement:

- PV often not involved in due diligence or contract development with third parties
- To ensure compliance, a template / generic agreement should be prepared by legal / PV, approved by management
  - To be used before detailed a safety agreement can be completed
  - Should be general enough to comply with regulatory requirements
  - Must include the exchange modalities of SAEs from clinical trials and AEFIs from any source, including the regulatory reporting responsibility
  - Must include the modalities of any regulatory submission (PSURs, DSURs, Annual Reports and their local requirements
  - Must include a statement that a safety section is needed and by when a formal and detailed safety agreement will be completed and signed by the safety groups (e.g., stand-alone Safety Data Exchange Agreement as Appendix)

# Why written Agreements?

- Remain compliant with Health Authority requirements
- Guidance and instructions to all involved parties in regard to their responsibilities for vaccine safety
- Ensure that all parties receive the safety documents they need to remain in full compliance with all regulatory and legal requirements in their jurisdiction of sale or study
- Ensure that adequate signaling is done and benefit-risk analyses are incorporated as complete as possible
- Ensure that product labeling is best possible the protect vaccinee / public health
- Have data ready for audits of inspections
- Have data available for any kind of vaccine crisis situations

# Written Agreements with Business Partners

- What and when does data get exchanged
  - Serious AEFIs or all EFIs
  - AEFIs sent to business are actually received (receipt date)  and vice versa
  - Timelines for sending serious AEFIs
  - Timelines must facilitate compliance with reporting requirements
- Who keeps and maintains the safety database
- How are Heath Authority queries and requests handled
- Who prepares aggregate reports (PSURs / PBRERs / DSURs) for Regulatory Reporting
- How are the individual AEFIs and aggregate reports submitted to Regulatory Agencies
  - Who is responsible
  - Timelines, method, format of submission, submission confirmations
- Who does signal management, safety review and risk management
- What provisions ensure that terms of the agreement are met?
  - Reconciliation of data, meetings, audits of business partner

# Example TOC of a Safety Data Exchange Agreement

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Parties / Scope / Effective Date of Safety Agreement

1. Purpose
2. Compliance with applicable law and Regulations
3. Scope
4. Language of exchange
5. Definitions
6. Exchange of single case adverse event information
7. Literature reports
8. Signal detection, safety issues and crisis management
9. Development Risk Management Plan (dRMP) / Risk Management Plan (RMP)
10. Expedited reporting of AEFIs to regulatory authorities
11. Reporting to investigators / ethics committee
12. Regulatory Authority enquiries
13. Standard reference documents
14. Contact persons
15. Global safety database
16. Ongoing evaluation of benefits and risks / Signal management
17. Audit / Inspection
18. Amendments to the agreement
19. Termination
20. Obligations surviving termination of this agreement
21. Signature

# Continuous Quality Improvement also in Pharmacovigilance