Vaccine Pharmacovigilance from Industry Perspective: Pre- and post-licensure

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Perception of pharmaceutical industry by the public

What are the Regulatory Authority Perceptions / Public Perceptions?

• “Industry hides its safety skeletons under the carpet”
• “Industry misleads doctors”
• “Industry publishes only positive trial data”
• “Negative trial data withheld”
• “Sponsors get the answers they want”
Changing Environment

- Harmonization efforts between different countries – ICH (International Council on Harmonization)
- Increased communications and collaboration between Regulatory Authorities and with supranational organizations (WHO, PAHO)
  - Consistent standards and harmonization
  - Exchange data and information
  - Data sharing / data transparency
  - Joint reviews
- Rational regulatory decision making
- Effective information dissemination to involved stakeholders

Increased scrutiny by regulatory, scientific and consumer communities concerning the safety profile of vaccines:
Pharmacovigilance is a key responsibility for all vaccine manufacturers

- Legally responsible for quality, safety and efficacy
- Regulatory requirement and a shared responsibility
- Pro-active, continuous monitoring of safety and effectiveness
- Ensuring positive benefit risk balance during whole life-cycle
- Ensuring lot-related safety
- Detection and evaluation of signals
- Communication: Respond to safety issues and crisis
Good Pharmacovigilance Practice Framework

An appropriate pharmacovigilance system relies on:

1. Collection, processing, and reporting of safety data
2. Continuous signal detection and benefit-risk assessment, as well as regular assessment of a product's safety by a Safety Management Team with escalation to senior management (Safety Board)
3. Proactive and timely communication of safety-relevant information based on awareness of pharmacovigilance and appropriate training
4. Quality management of pharmacovigilance procedures

Includes all stages of medicinal product development and life cycle

Follows Good Pharmacovigilance Practice:

- Regulatory reporting (individual / periodic reports)
- Safety surveillance of the product during its whole life cycle:
  - Signal management
  - Risk management
  - Risk minimization
  - Risk communication
Good Pharmacovigilance Practice
Basic principles for industry

Pharmaceutical Companies must have a Pharmacovigilance System in place which is:

**effective**
- rigorous alerting, signal detection and handling

**efficient**
- focus on „important“ (e.g., serious, unexpected reactions)

**consistent**
- one corporate opinion on the nature and level of causality of the reaction

**valid**
- evaluation and assessment tools yield correct results
Good Pharmacovigilance Practice
Regulatory requirements

Upper management should provide leadership in the implementation of the quality system.

All persons in the entire organization should engage in continuous improvement.

All available evidence on benefit-risk should be sought and all relevant aspects having an impact on the benefit-risk balance should be considered for decision making.

All persons within the organization should be involved and support the PV system according to their tasks and responsibilities.

Resources and tasks should be organized as structures and processes to support the proactive, risk-proportionate, continuous and integrated conduct of PV.

Good cooperation should be fostered between all stakeholders.
Good Pharmacovigilance Practice
Current issues in emerging countries

- PV still in infancy
  Act when legally required
- Not enforced through regulation
- Minimal efforts in risk identification, assessment and management
- Focus on data collection
- Quality Systems and Processes to evolve
- No common understanding of vaccine safety and safety data quality
### CIOMS Working Group Reports on Pharmacovigilance

<table>
<thead>
<tr>
<th>Report Number</th>
<th>Title</th>
<th>Final Report Year</th>
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<tbody>
<tr>
<td>CIOMS I</td>
<td>International reporting of adverse drug reactions</td>
<td>1990</td>
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<tr>
<td>CIOMS II</td>
<td>International reporting of periodic drug-safety update summaries</td>
<td>1992</td>
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<tr>
<td>CIOMS III</td>
<td>Guidelines for preparing core clinical safety information on drugs</td>
<td>1995 / new proposals 1999</td>
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<tr>
<td>CIOMS V</td>
<td>Current challenges in pharmacovigilance: pragmatic approaches</td>
<td>2001</td>
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<td>CIOMS VI</td>
<td>Safety monitoring and evaluation during clinical trials</td>
<td>2005</td>
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<tr>
<td>CIOMS VII</td>
<td>Development Safety Update Report</td>
<td>2007</td>
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<tr>
<td>CIOMS VIII</td>
<td>Signal Detection</td>
<td>2010</td>
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<tr>
<td>CIOMS IX</td>
<td>Practical Approaches to Risk Minimisation for Medicinal Products</td>
<td>2014</td>
</tr>
<tr>
<td>CIOMS SMQ</td>
<td>Implementation: Development and Rational use of Standardised MedDRA Queries (SMQs)</td>
<td>2016</td>
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Each report represents a significant milestone in the development of Pharmacovigilance leading to ICH Guidelines.
ICH International Council for Harmonization

Applicable Guidelines Pre- and Post-licensure

E2A: Definitions and Standards for Expedited Reporting
E2B: Data Elements for Transmission of ADR Reports
E2C: Periodic Safety Update Reports (PSUR)
E2D: Post approval of safety data management
E2E: Pharmacovigilance planning (Risk Management Plan)
E2F: Development Safety Update Report (DSUR)
E6 (R2): Good Clinical Practice (5.16/5.17/6.8)
M1: Medical Terminology: Medical Dictionary for Regulatory Activities Terminology (MedDRA)

ICH brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration, and to promote greater harmonization through the development of technical Guidelines and requirements for pharmaceutical product registration.
Important definitions

Definitions in national legislation are in general consistent (not verbatim) with ICH definitions (ICH E2A and ICH E6)
Pharmacovigilance Regulations

Pre-licensure Clinical trials

• EU Regulations:
  • Council Directive 2001/20/EC (Clinical Trials)
  • EUDRALEX Volume 10: Clinical Trials, Notice to applicants (July 2006), Chapter II: Safety section with Detailed Guidance 2011/C172/01 2011 – “CT-3”
  • EudraCT Database and EU CTR (Clinical Trial Registry)

• USA Regulations:
  U.S. Title 21 Code of Federal Regulation:
  21 CFR 310 (New drugs)
  21 CFR 312 (Investigational new drug application)

• National Regulations:
Pharmacovigilance Regulations

Post-licensure

- **EU Regulations:**
  - Council Directive 2001/83/EC and
  - Regulation EC/726/2004 and
    - Regulation EU/1235/2010
  - Good Vigilance Practice (GVP): 15 Modules
  - GVP P I: Product- / population specific considerations – Vaccines for prophylaxis against infections disease

- **USA Regulations:**
  - U.S. Title 21 Code of Federal Regulation:
    - CFR 600.80, FDA Guidance on ADR reporting

- **National Regulations:**
Pharmacovigilance Framework
Responsibilities of the Company

Marketing Authorization Holder (MAH) must ensure that there is an appropriate system in place to assure responsibility and liability for their products world-wide and to ensure that appropriate actions can be taken any time.

MAH must have a qualified person responsible for pharmacovigilance (QPPV)

In the EU the QPPV acts as a single point of contact for Health Authorities 24/7 (GVP Module I)

QPPV Responsibilities:
• Establishing and maintaining the company’s appropriate pharmacovigilance system
• Preparing pharmacovigilance reports as defined by regulations
• Answering requests from Health Authorities
• Providing Health Authorities with any other information relevant to product safety
Pharmacovigilance Operating Model Framework

- **PV Strategy**
  - Best use of PV within the company:
    - Not only as a mechanism to ensure compliance and mitigate risk, but develop a safety strategy (e.g., alignment with product strategy balanced against risks)

- **Capabilities**
  - Primary capabilities: Case management, aggregate reporting, signal intelligence, risk management:
    - Resources to be used most efficiently for required capabilities and regulatory requirements

- **Network**
  - Distribution of PV activities across the globe to best use resources:
    - Flexible organizational structure to address differences in local PV / regulatory reporting requirements

- **Governance**
  - Mechanisms in place to escalate / resolve PV / safety issues to the right level of management:
    - Effective governance with well defined roles, responsibilities, metrics, processes and structure
Pharmacovigilance activities
Shift from developing to mature PV organization

Developing PV Organization

- Low Strategic Focus
- High Effort Expended
- Aggregate Reporting
- Case Management
- Signal Intelligence
- Risk Management

Mature PV Organization

- High Strategic Focus
- Low Effort Expended
- Aggregate Reporting
- Case Management
- Signal Intelligence
- Risk Management

DCVMN PV Training March 2021 Hartmann
Pharmacovigilance activities
Medical Safety activities in pre- and post-licensure

<table>
<thead>
<tr>
<th>Management of all safety matters</th>
<th>Medical assessment of individual safety information (e.g., AEFIs/ICSRs, SAEs, AESIs/IMEs,)</th>
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<tbody>
<tr>
<td>Safety surveillance: signal detection, labeling for RSI, DCSI, CCSI, SPC</td>
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<td>Regulatory safety compliance</td>
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<td>Risk management (including EU-RMPs / DRMPs and REMS)</td>
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<td>Review / sign off the Safety Sections of all Clinical Trial Documents (e.g., IB, synopsis, clinical trial protocol, CRF, ICF, SAP, CSR)</td>
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<td>Handling of Urgent Safety Measures</td>
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<td>Oversight over all vaccine safety matters</td>
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<tr>
<td>Escalation of safety issues to Senior Management (e.g., Safety Board)</td>
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<td>Safety-related communication (internal &amp; external stakeholders)</td>
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Pharmacovigilance activities
Operational and QA activities

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<thead>
<tr>
<th>Management of operational / QA (compliance) pharmacovigilance activities:</th>
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<tr>
<td>Case handling process</td>
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<tr>
<td>Safety Database</td>
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<tr>
<td>Regulatory safety compliance</td>
</tr>
<tr>
<td>Regulatory Intelligence</td>
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<tr>
<td>Compliance management</td>
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<tr>
<td>PV training: internal / cross functional</td>
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<tr>
<td>Record management</td>
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<tr>
<td>Monitoring performance and effectiveness</td>
</tr>
<tr>
<td>Safety Data Exchange Agreements with third parties</td>
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<tr>
<td>Audit / Inspection readiness</td>
</tr>
<tr>
<td>Business continuation</td>
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<tr>
<td>Crisis management / Preparedness planning</td>
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Operational Overview of Pharmacovigilance
Components / Capabilities of a complete PV System

Activities may be performed by different departments or outsourced to CROs. Different functions may be performed by the same person, qualified / trained for performing the activity.
Collection of AEFIs in clinical trials
ICH E6 GCP sections 5.16 / 5.17 / 6.8

- Protocol must describe how AE will be collected and how subjects will be asked for AEs, hospitalisation, doctor visits and other relevant medical occurrences.

- Non-serious AEs must be reported by the investigator in a CRF (“case report form”).

- SAEs (“serious adverse events”) and protocol-specific AEs must be collected on a special form (SAE reporting form).

- Diagnosis to the reported signs and symptoms should be added.

- Follow-up time for AEs must be described.

- Underlying or pre-existing diseases must be documented (“medical history form”).

- All AEs must be assessed regarding seriousness, expectedness and causality (“related”/”unrelated”).

- Responsibilities and time frames for reporting AEs must be defined.
Collection of AEFI\text{'s in post-licensure Source of data

- Spontaneous Reports
  - from health care providers
  - from regulatory agencies / WHO
  - From immunization programs
  - from patients / consumers
  - unsolicited communications
  - media, lay press
  - Internet

- Post-marketing Surveillance Studies (Phase IV; PASS, LSST)

- Epidemiologic studies (e.g., cohort studies, case control studies)

- Registries

- Literature Publications
Case management
Formal and content aspects

Information gathering
Determines data quality

Data entry / coding / assessment
Provides data for analysis

Analysis / signal detection / risk management
Content critical

Expedited / regulatory reporting
Compliance critical
Pharmacovigilance Responsibilities Depending on status of licensure

Market Authorization Holder (MAH) is legally responsible for Pharmacovigilance.

- UN Agencies
  - UNICEF
  - WHO prequalified
    - Manufacturer responsibility

- Country F:
  - Licensure relies on license in Country of origin
    - MAH: Manufacturer

- Country E:
  - License relies on EU Article 58 Regulation / WHO prequalification
    - MAH: Manufacturer

- Licensed in Country of origin
  - MAH: Manufacturer

- Licensed in Country A
  - MAH: Distributor A

- Licensed in Country B
  - MAH: Distributor B

- Licensed in Country C
  - MAH: Local Operating Company (LOC 1)

- Licensed in Country D
  - MAH: Local Operating Company (LOC 2)
WHO / CIOMS Vaccine Pharmacovigilance Guidance
CIOMS / WHO Working Group Reports on Vaccine Pharmacovigilance

Definition and Application of Terms for Vaccine Pharmacovigilance (2012)


To propose
- Standardization of definitions to monitor vaccine safety pre- and post-licensure

To contribute
- To the development, review and approval of AEFI case definitions
- Brighton case definitions to the dissemination and use of AEFI case definitions

To collaborate
- With other CIOMS working groups (WG):
  ✓ MedDRA WG
  ✓ CIOMS WG VIII on Signal Detection relevant to vaccine safety
Parties in Global Vaccine Safety
Regional and international awareness and collaboration

CIOMS Guide to Active Vaccine Safety Surveillance 2017
WHO and Vaccine Pharmacovigilance

- Global Advisory Committee on Vaccine Safety (GACVS)
  - Provides independent scientific advice to WHO
  - Established to respond efficiently to vaccine safety issues
- Global Vaccine Safety Initiative (GVSI) 2012 - 2020
  - Founded in 2011 to implement strategic plan for strengthening vaccine safety globally (“Vaccine Safety Blueprint”)
  - Minimal capacity for all
  - Network for enhanced vaccine pharmacovigilance
  - Global support structure

**Mission**
To optimize the safety of vaccines through effective use of pharmacovigilance principles and methods.

**Vision**
Effective vaccine pharmacovigilance systems are established in all countries.

**Strategic Goals**
- To assist low and middle income countries (LMIC) to have at least minimal capacity for vaccine safety activities.
- To enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines.
- To establish a global vaccine safety support structure.
Reflections on Pharmacovigilance in Industry

Companies most often managed by non-medically trained managers:

• Senior manager’s view on vaccine safety can be vague, ill-defined or not understood

Regulation governing vaccine safety are highly technical and difficult to understand

• Managers prefer “Executive Summaries” that may not capture the nuances of clinical judgement
• Legal discouragement about written documents on real or potential safety concerns

Pharmacovigilance is a cost center, not a profit center

• Proactive pharmacovigilance promotes reputation with authorities and can prevent safety concerns becoming safety crisis (“safety sells”)

Pharmacovigilance is often not well funded

• Vaccine crisis and public awareness as well as antivaccinist’s movements matter and may increase funding
Reflections on Pharmacovigilance in Industry

Pharmacovigilance has a wallflower image in some companies

- PV must report into medical research or regulatory departments which are empowered and have organizational voice

Performance measurements (i.e., on-time reporting and submission) captures mechanical performance, not medical protection and risk management aspects

- Satisfaction of Health Authorities with company’s PV performance difficult to measure

Management often thinks a serious safety issue must be proven by hard data with clear causality

- The vaccine may be the cause of the problem, even if we know that there are other possible causes

- Create a safety culture throughout the company
- Integrate vaccine and vaccinees safety into company’s responsibility
Pharmacovigilance - a Life Cycle Approach

- Pharmacovigilance works towards integrated and proactive safety surveillance to protect patients, products and company assets
- Effective and efficient vaccine safety monitoring systems should be in place to detect new risks and identify new information about known risks
- Pharmacovigilance is a shared responsibility
- Confidentiality and transparency is important
- Product stewardship is crucial
Pharmacovigilance in Industry

More regulations
More processes
More confusion
More inspections
More findings