Developing Countries Vaccine Manufacturers Network

Vaccine Safety Monitoring
DCVMN Regional Training Workshop
Sao Paulo 27 - 30 May 2019

Pharmacovigilance from Industry Perspective

Pre- and Post-Licensure

Katharina Hartmann, PharmD

Former Senior Lecturer Pharmacovigilance and Pharmacoepidemiology, ETH Zürich
Former Global Head Pharmacovigilance Takeda Vaccines
Former Global Head Pharmacovigilance Crucell / Berna Biotech
Former Member of the WHO / CIOMS Vaccine Safety Working Group

What is Pharmacovigilance?

WHO Definition:

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Vaccine pharmacovigilance is the science and activities relating to the detection, assessment, understanding, prevention and *communication* of adverse events *following immunization or any other possible vaccine - or immunization-related problems.*

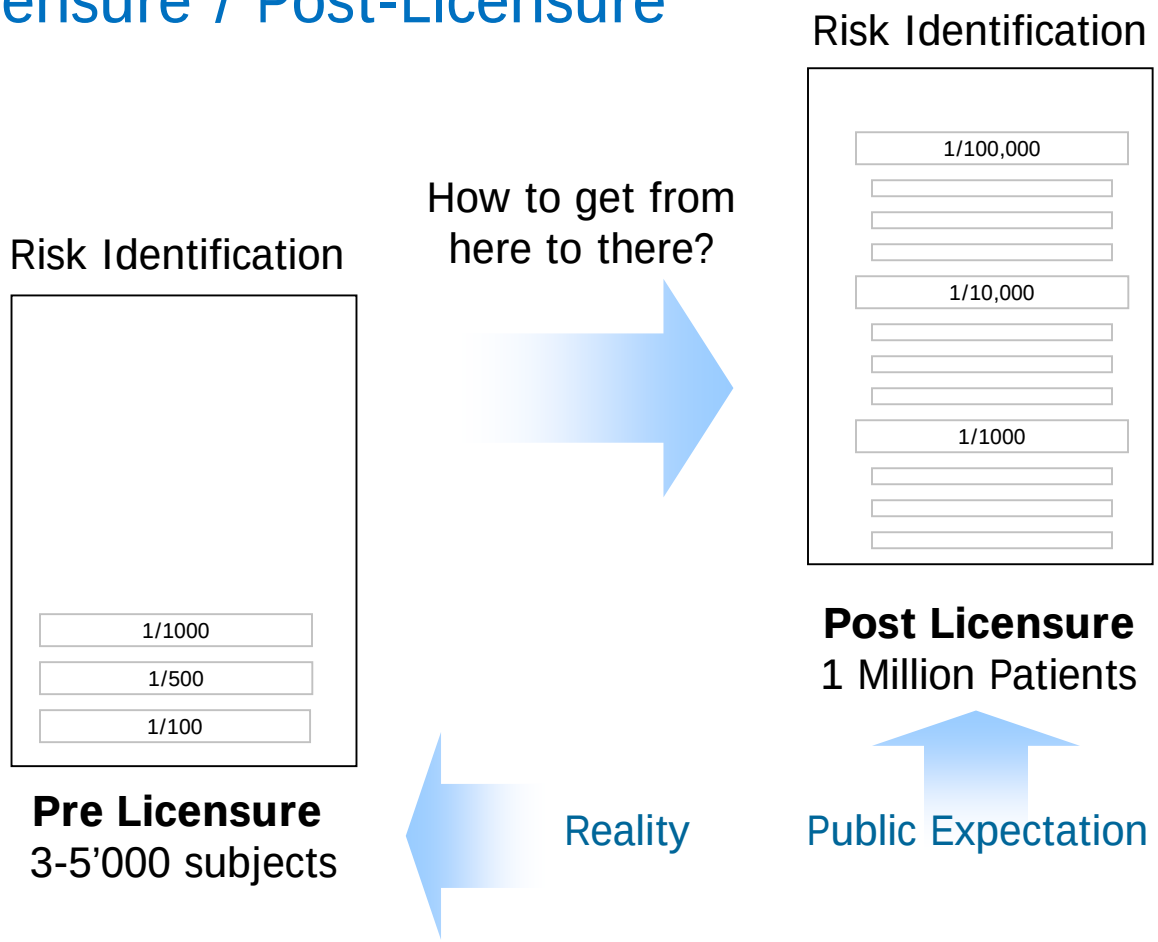
Why Pharmacovigilance?

- Pharmacovigilance (PV) is a global public health activity and includes all stakeholders
- Vaccine Pharmacovigilance is a key responsibility for all vaccine manufacturers:
  - Manufacturers are legally responsible for the vaccine quality, safety and efficacy
  - PV is a shared responsibility, not only a regulatory requirement
  - Lower risk tolerance: vaccine < 1:100`000 versus drug 1:10 – 1:1`000
  - Proactive vaccine safety surveillance during the whole life-cycle is vital and indispensable:
    - To protect the vaccinated individuals as well as the population from harm
    - To ensure lot-related safety
    - To ensure ongoing effectiveness
    - To ensure continuous positive benefit risk ratio
    - To clarify signals from individual AEFIs
    - To be able to react to changes of the benefit risk ratio
    - To protect the vaccine from false positive signals (i.e., to keep the vaccine on the market)
    - To respond to safety crisis (e.g., Quinvaxem safety crisis in Vietnam)

Lessons learned from Vaccine Issues
Examples

1926	**Diphtheria toxin:** Diphtheria-toxin mediated disease due to incomplete inactivation of toxin (safety testing of every lot)
1929	**BCG:** contaminated BCG strain led to deaths of at least 72 infants in Germany
1942	**Yellow fever:** contaminated human serum used as vaccine stabilizer: approx. 28'000 hepatitis B cases (quality control of additives)
1955	**Poliomyelitis:** Cutter incident involving incomplete inactivation of vaccine resulting in 51 vaccinees permanently paralyzed, incl. 5 deaths (scaling up can create problems)
1960s	**Poliomyelitis:** Some early oral poliovirus vaccine (OPV) lots contaminated with oncogenic monkey virus (simian virus 40)
1980 – 1990s	**Measles:** "excess mortality" in children who received high titer measles vaccines (safety in one population ≠ safety in all)
> 1981	**Hepatitis B:** processing of plasma-derived vaccines containing viruses unknown at the time (e.g. HI virus, hepatitis C virus)
1999	**Rotavirus vaccine:** withdrawal due to intussusception in vaccinated infants

Why Pharmacovigilance?
Pre-Licensure / Post-Licensure



- Before vaccines are licensed they are tested in randomized clinical trials.
- Randomized trials are designed to test the efficacy of a product.
- They involve relatively small numbers of individuals.
- The individuals involved in clinical trials may not be representative.

Objectives of Pharmacovigilance /1

Physicians / patients:

assure quality, efficacy AND safety of product

Pharmaceutical industry:

proactive safety monitoring during whole life cycle to ensure patient safety

product protection (clarify false positive ADR signals)

Regulatory Agencies:

on-going risk/benefit evaluation

safe products on the market

Objectives of Pharmacovigilance /2

- Continued monitoring of the vaccine products as used in everyday practice to timely identify previously unrecognized or changes in the patterns of their adverse effects
- Assessing the risks and benefits of products in order to determine what action, if any, is necessary to improve their safe use throughout the product‘s life cycle
- Providing information to users to optimize safe and effective use of products
- Refutation of „false-positive“ signals arising in the professional or lay media or from spontaneous reports.
- Monitoring the impact of any action

Challenges for vaccine safety

Examples

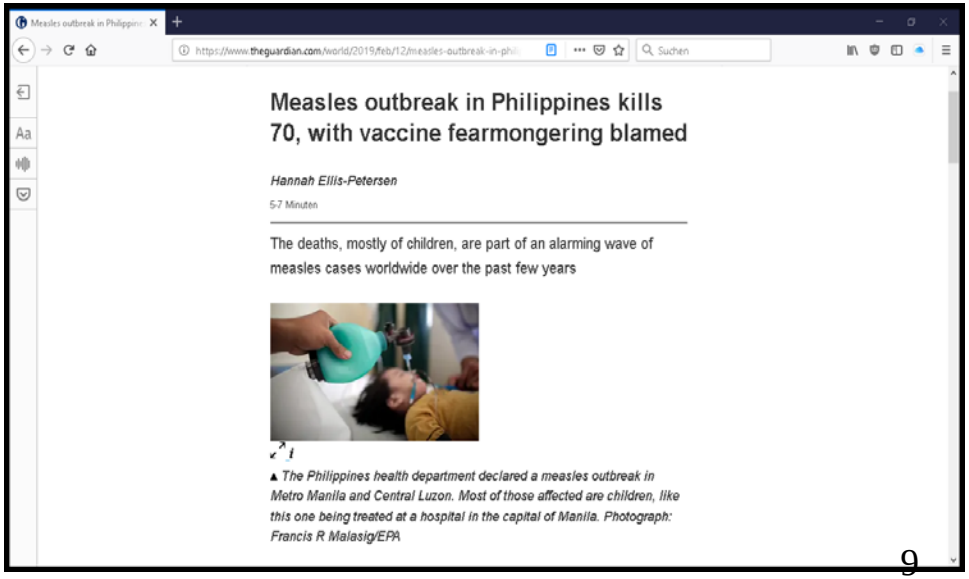
- Continued prevalence of unsafe injections and injection practices
- Mishandling of rumors and adverse events
- Lack of access to newer, safe technologies such as auto-disposable syringes
- Growing anti-immunization movements, including anti-vaccination websites
- Inadequate AEFI surveillance
- Globalization and the internet with greater impact of misinformation raising public concerns about harm from vaccines

Pharmacovigilance – The Current Environment

Developing Countries Vaccine Manufacturers Network

Vaccine safety in the Spotlight

- ... in the media
- ... high on the regulatory agenda
- ... generally reactive



Pharmacovigilance

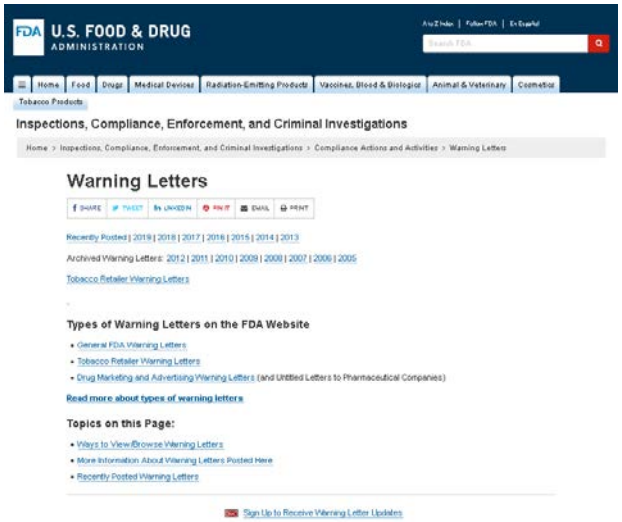
Perception of Industry by the public

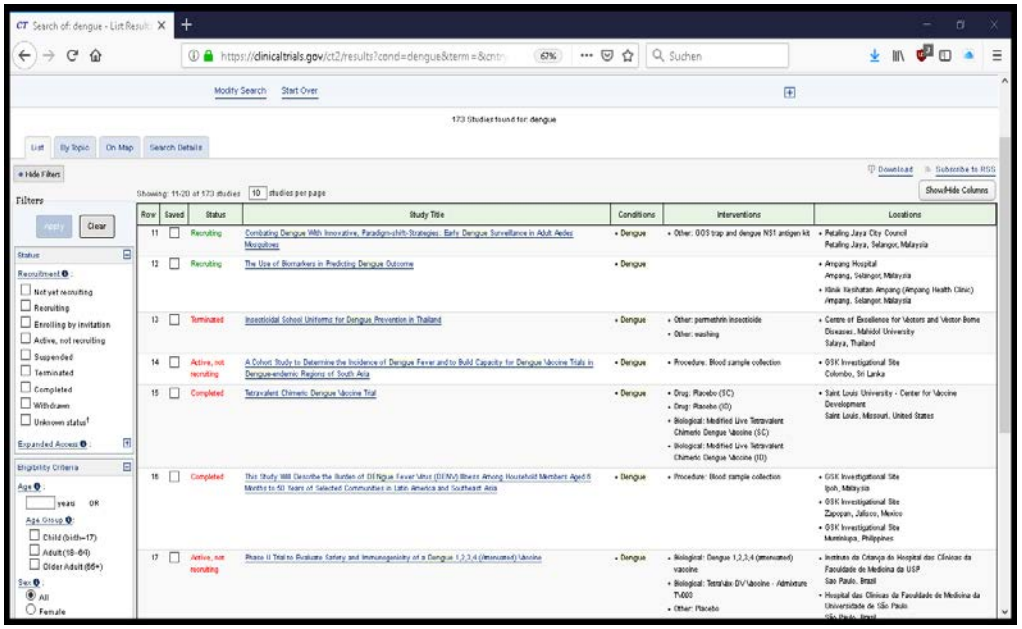
Regulatory Authority Perceptions / Public Perceptions?

- “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”

www.clinicaltrials.gov

FDA Warning Letters

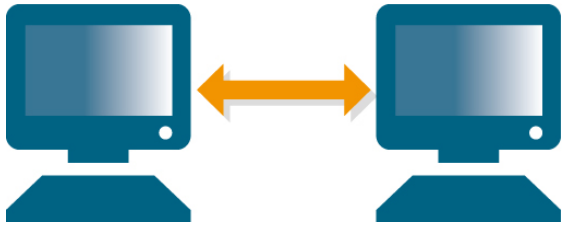




Changing Environment

Increased scrutiny by regulatory, scientific and consumer communities concerning the safety profile of vaccines:

- Harmonization efforts between different countries – ICH (International Council on Harmonization)
- Increased communications and collaboration between Regulatory Agencies 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



Pharmacovigilance Regulations
Start and maturing

1937	FDA toxicity studies for excipients (sulfanilamide-elixir)
1950	Introduction of registries (Chloramphenicol)
1961	Spontaneous reporting schemes (thalidomide catastrophy)
1967	WHO ADR Drug Monitoring System (WHO Resolution 20.51)
1976	EU Directive 75/319 EEC Article 29A: System set up to collect information useful in surveillance of medicinal products, in particular with regard to adverse reactions
1986	CIOMS initiated CIOMS I Working Group
>1990	Harmonisation of pharmacovigilance
1995	ICH Guidelines
1995	EMA (European Pharmacovigilance Regulations)
2001	EU Directives / Eudralex: Volume IX Pharmacovigilance
2004	EUDRACT / Eudravigilance
2007	Eudralex: Volume 9A Pharmacovigilance
2010	New EU Pharmacovigilance Directive and Regulations
2012	Implementation of the new EU Legislation: Good Vigilance Practices GVP

ICH International Council for Harmonization

Harmonization Efforts

E2A:	Definitions and Standards for Expedited Reporting
E2B:	Data Elements for Transmission of ADR Reports (Maintenance) including M2
E2C:	Periodic Safety Update Reports (PSUR)
E2D:	Post approval of safety data management
E2E:	Pharmacovigilance planning (Risk Management Plan)
E2F:	Development Safety Update Report

E3:	Clinical Study Reports
E6:	Good Clinical Practice
E17:	General Principles for Planning and Design of Multi-Regional Trials
E19:	Optimization of Safety Data Collection

M1:	Medical Terminology: Medical Dictionary for Regulatory Activities Terminology (MedDRA)
M2:	Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)
M4:	Common Technical Document (CTD)
M8:	Electronic Common Technical Document (eCTD)

Pharmacovigilance Guidelines
Pre-Licensure - Clinical trials

ICH Guidelines

EU Guidelines:

- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/E (will replace Directive and Detailed Guidances 2019)
- Council Directive 2001/20/EC (Clinical Trials)
- EUDRALEX Volume 10: Clinical Trials, Notice to applicants (July 2006), Chapter II:
  - Monitoring and Pharmacovigilance:
    - Detailed Guidance 2011/C 172/01, OJ June 11, 2011 (Collection, verification and presentation of AE/ ADR reports from clinical trials on medicinal products for human use "CT-3")
    - Detailed Guidance ENTR/CT4, Revision 1, April 2004 (Eudravigilance – Clinical Trial Module)

USA Guidelines:

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

National Guidelines

Pharmacovigilance Guidelines
Post-licensure

ICH Guidelines

EU Guidelines:

Council Directive 2001/83/EC (Community code relating to medicinal products for human use) and

Councel Directive 2010/84/EU

Regulation EC/726/2004 and

Regulation EU/1235/2010

Good Vigilance Practice (GVP): 15 Modules incl. Annexes and Product-specific considerations P I1 (vaccines), P II (biologicals) and P IV (Pediatric Population)

USA Guidelines:

U.S. Title 21 Code of Federal Regulation:

21 CFR 310.305; 21 CFR 312.32; 21 CFR 314.50; 21 CFR 314.80; 21 CFR 600.80, FDA Guidance on ADR reporting

National Guidelines

Product-specific considerations (EU GVP P I):
PV for vaccines for prophylaxis

Objective is to strengthen the conduct of PV for vaccines, does NOT replace the information provided in the other EU GVP modules.

- Module relevant to vaccines used in pre- and post-exposure prophylaxis of infectious diseases.
- Module focuses on vaccine-specific aspects to be respected when designing and implementing PV activities for vaccines.
- Module provides guidance specific for vaccines in relation to PV processes described in the following GVP Modules:
  - Module V: Risk Management System
  - Module VII: Periodic Safety Update Report
  - Module VIII: Post-authorisation Safety Studies
  - Module IX: Signal Management
  - Module XV: Safety Communication
- Module provides guidance on „Batch recall and quarantine“ (legal basis: EMA GMP and GDP compliance)

➡ Implicates that the MAH must have a specific PV system for vaccines established

Pharmacovigilance: HOW?
GPvP (Good Pharmacovigilance Practice)

The Pharmacovigilance framework

- includes all stages of medicinal product development and life cycle
  - pre-clinical
  - clinical: pre-licensure and post-licensure
- requires an appropriate PV* system
- follows Good Pharmacovigilance Practice (GPvP):
  - Regulatory reporting (expedited / periodic reports)
  - Surveillance of the product during its whole life cycle:
    - Risk management:
    - Risk minimization
    - Signal management

***Pharmacovigilance System**
In general, a pharmacovigilance system is a system used by an organization (company, regulator) to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of medicinal products and detect any change to their risk-benefit balance.

Good Pharmacovigilance Practice /1
Principles

- Effective Pharmacovigilance that meets national, international (e.g., ICH, FDA, EMA) and supranational (e.g., WHO, PAHO) requirements needs:
  - An adequate system
  - Defined processes
  - Trained personal
  - Quality assurance system
  - Documentation of the processes
  - Internal audits and documented training

Safety management 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 the Safety Management Team SMT with escalation to 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

Good Pharmacovigilance Practice /2

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“ reactions
- consistent:
  - one global corporate opinion on the nature and level of causality of the reaction
- valid:
  - evaluation and assessment tools yield correct results

Good Pharmacovigilance Practice /3

Current scenario in some developing countries

- Not enforced through regulations
- Still in it`s infancy, but maturing
- Quality systems and processes yet to evolve
- Focus is still on data collection
- Minimum efforts in risk identification, assessment and management
- Only act when legally required or required by regulators
- No common understanding of vaccine safety and safety data quality

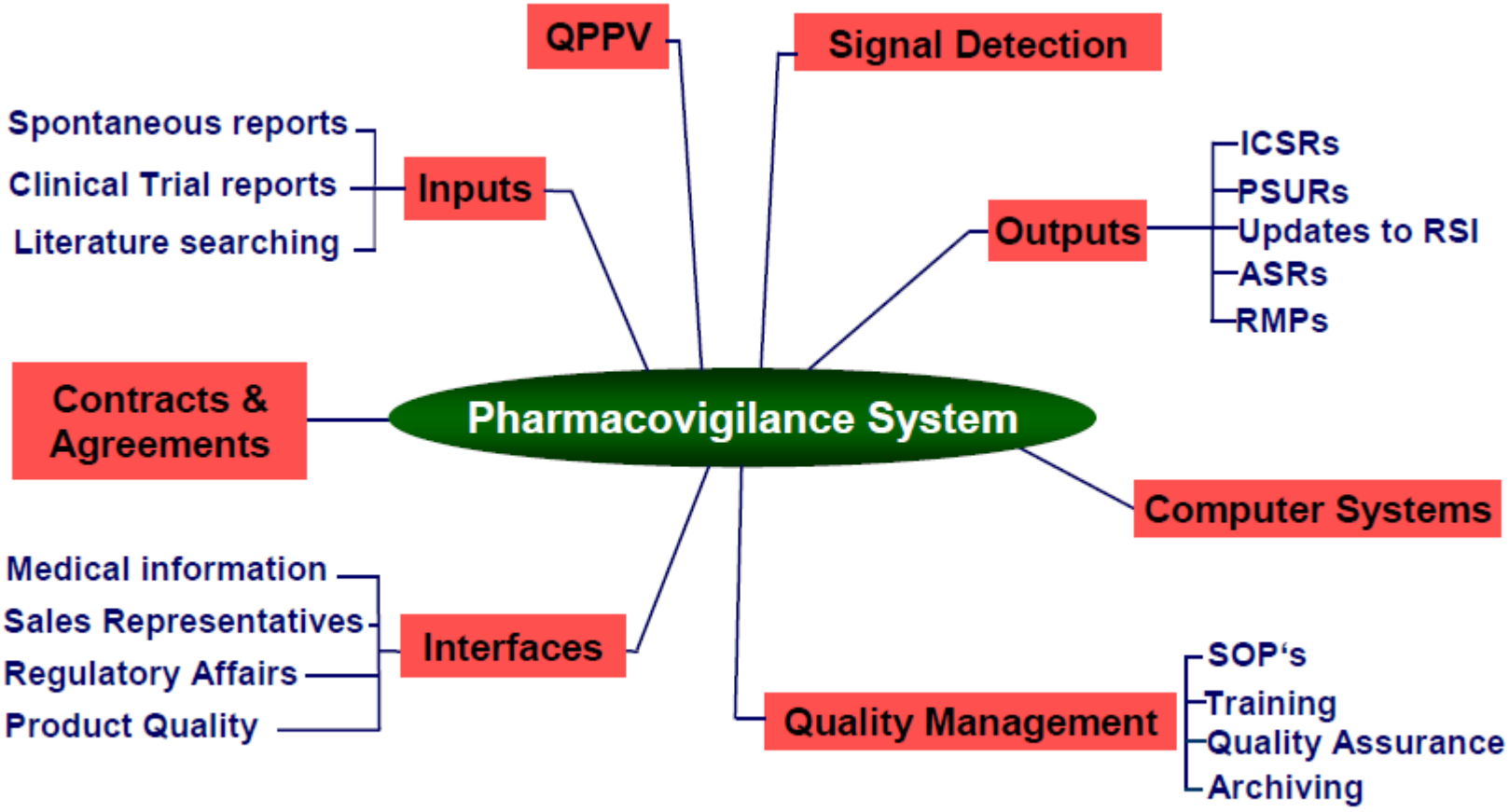
Pharmacovigilance framework
Responsibilities of the Company

- Manufacturer / 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
- Manufacturer / MAH must have a dedicated qualified person responsible for Pharmacovigilance*
- Manufacturer / MAH must
  - have a single system to collect and collate AEFIs
  - meet regulatory reporting requirements
  - ensure ongoing PV evaluation
  - ensure timely reaction on requests of Regulatory Authorities.

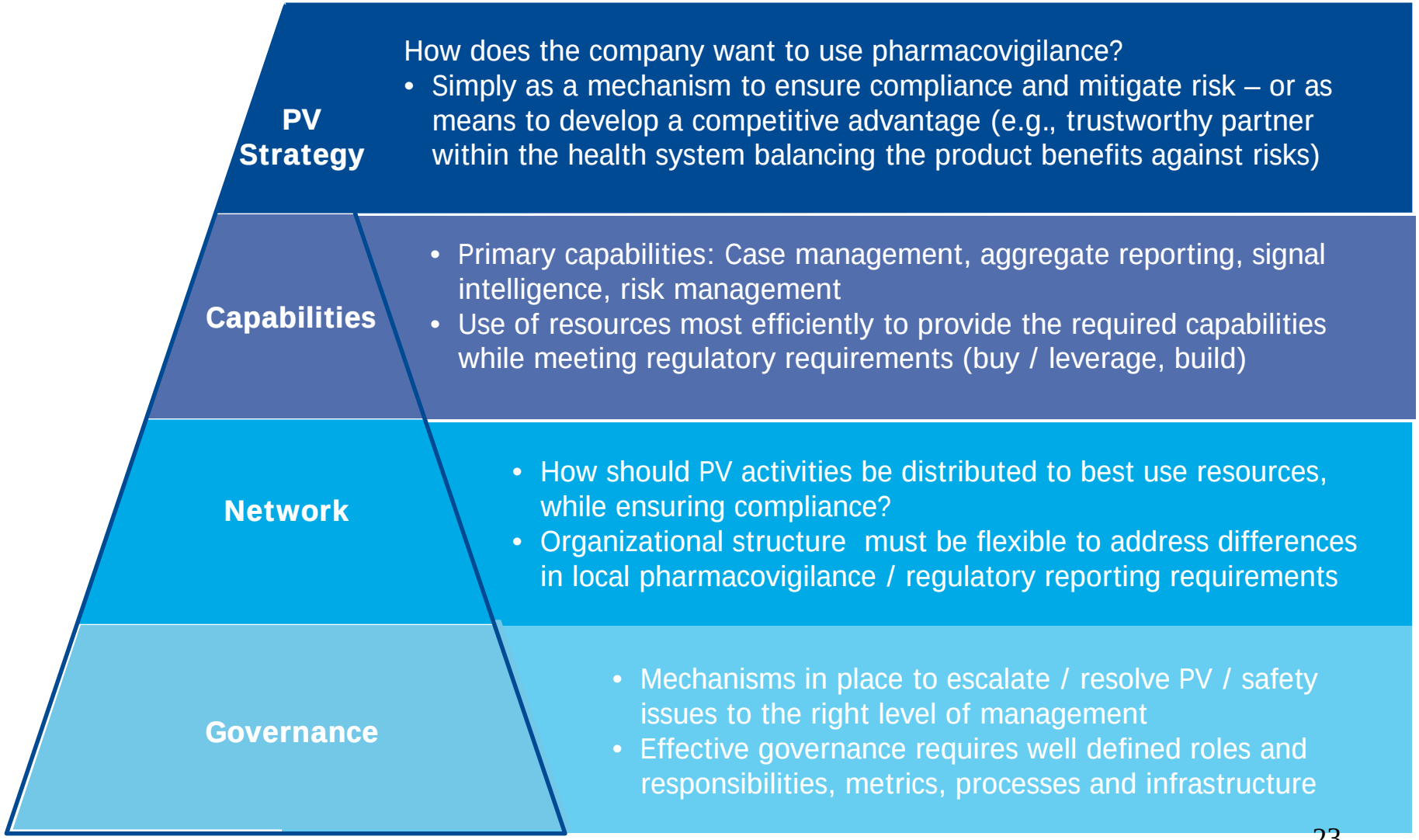
* In the EU this is the QPPV
QPPV must be available 24/7

Basis of a Pharmacovigilance System

To be tailored to the needs – one size does not it all



Framework of a PV Operating Model



Pharmacovigilance activities
Medical Safety activities

Management of all safety matters, incl. benefit / risk assessments, decisions, escalation and communication of safety information:

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

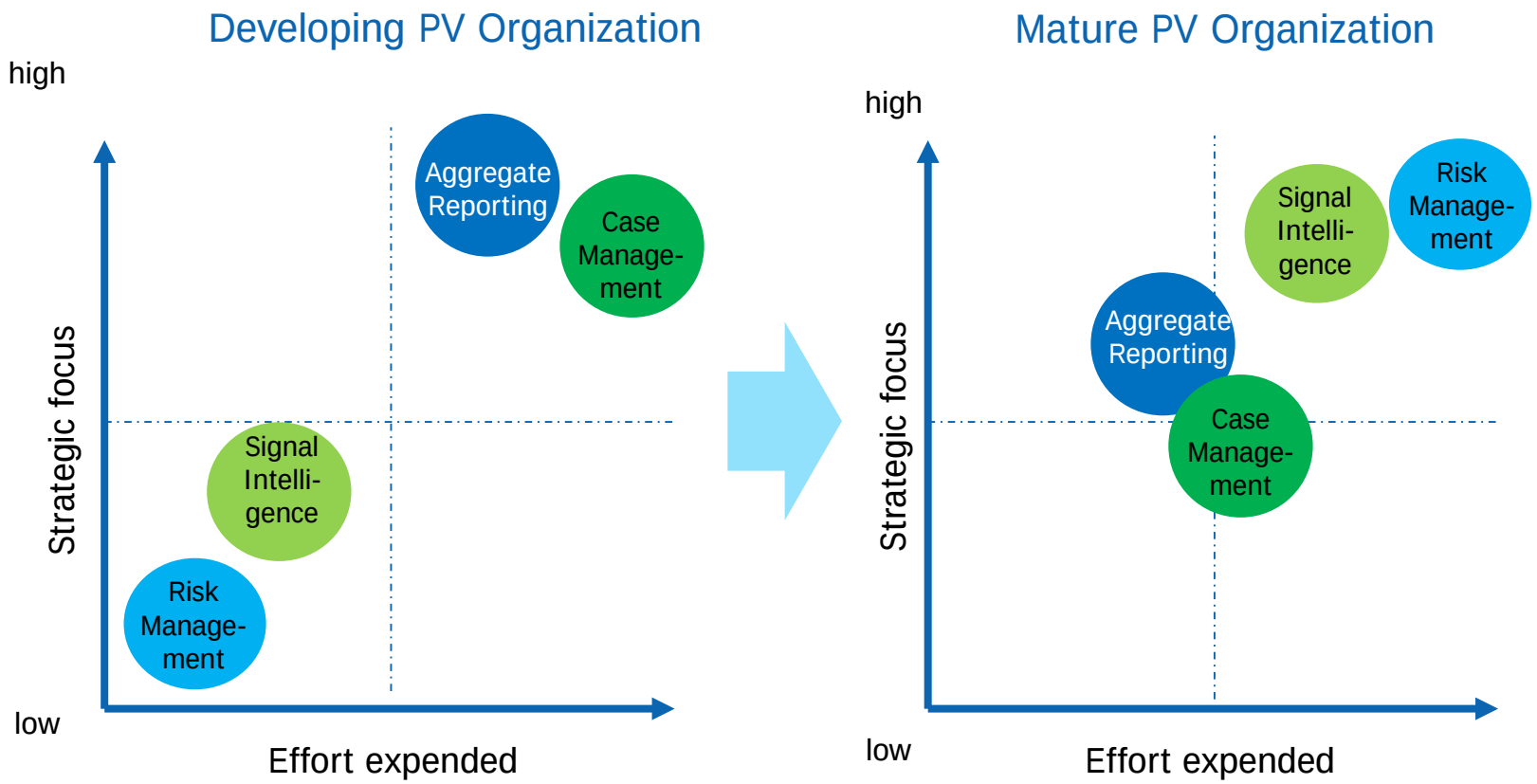
Pharmacovigilance activities
Operational / QA activities

Management of operational / QA (compliance) pharmacovigilance activities:

- Case handling process
- Safety Database
- Regulatory safety compliance
- Regulatory Intelligence
- Compliance management
- PV training: internal / cross functional
- Record management
- Monitoring performance and effectiveness
- Safety Data Exchange Agreements with third parties
- Audit / Inspection readiness
- Business continuation
- Crisis management / Preparedness planning

Pharmacovigilance activities

Shift from a developing to mature PV organization



Pharmacovigilance System
Description of an appropriate system

- Description of the organization and PV activities with documented procedures and defined processes:
  - Responsibilities of the Qualified Person Responsible for Pharmacovigilance
  - Management of Pharmacovigilance Data
  - Spontaneous Case Processing
  - Literature Searching
  - Periodic Safety Update Reports
  - Signal management / Evaluation of Safety Data
  - Risk Management Plans
  - Reference Safety Information
- Database
- Contractual Agreements for fulfillment of pharmacovigilance obligations
- Training
- Quality Management System

EU / EEA Member States:
Pharmacovigilance System Master File PSMF (GVP Module II)

Collection of AEFIs in clinical trials
ICH E6 GCP 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.

Regulatory - Legal Responsibilities: The sponsor is responsible for the ongoing Safety evaluation of the investigational product (ICH E6 5.16.1)

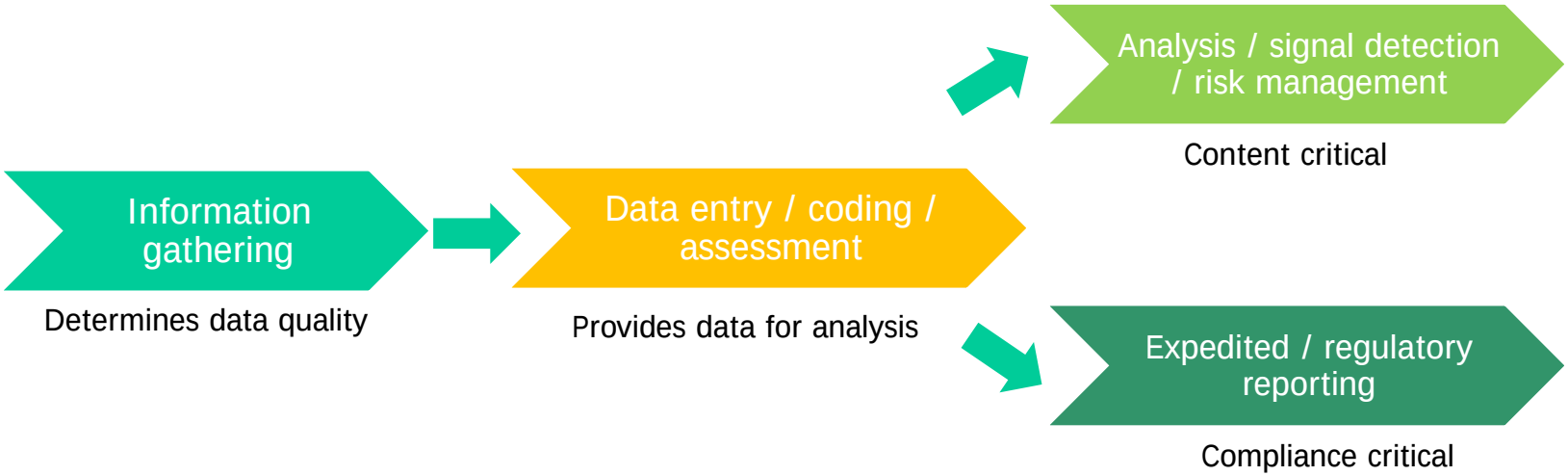
Collection of AEFIs in post-licensure
Source of data

- 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

Individual Case Safety Report
Analysis of the reported data

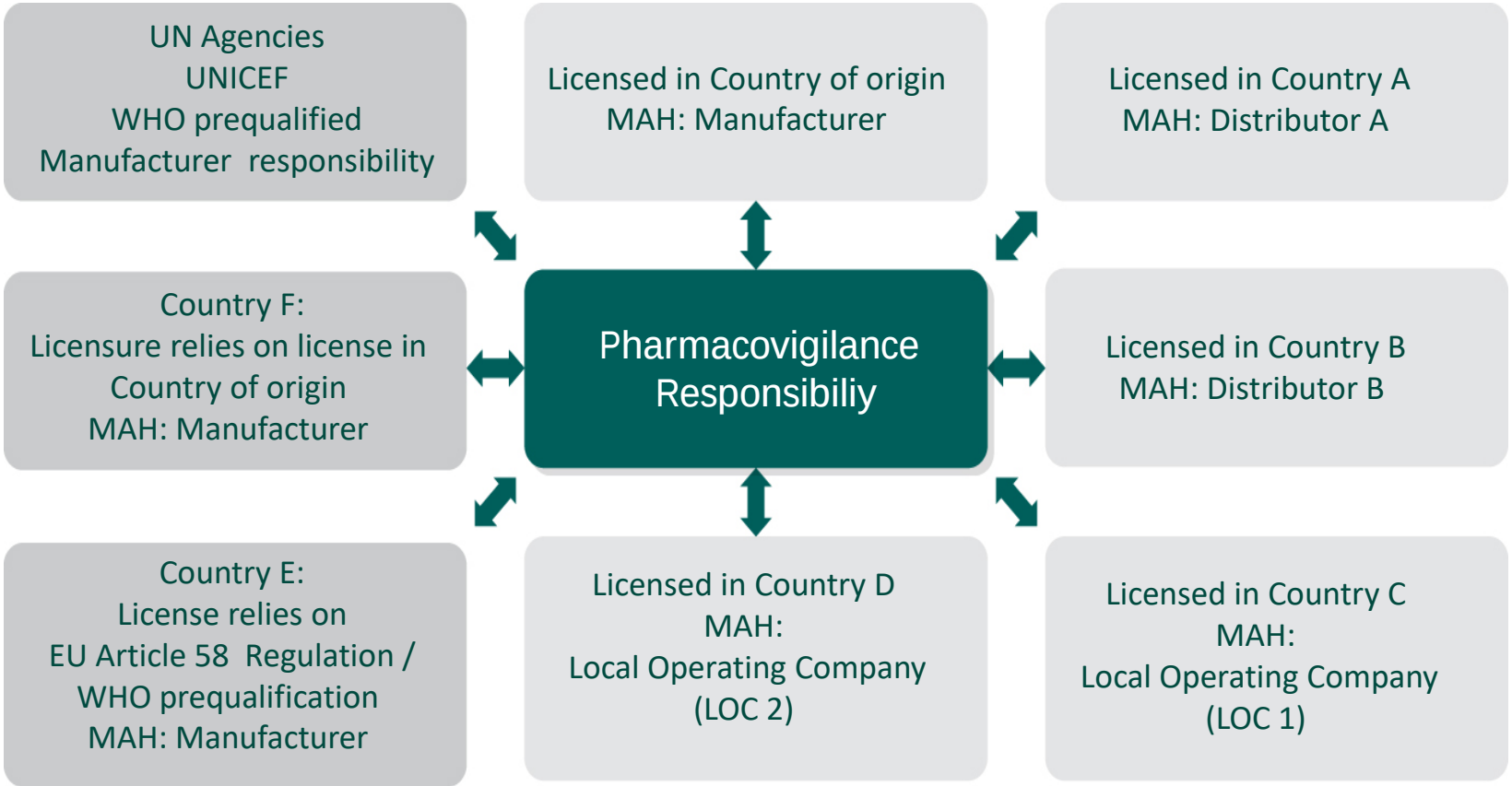
- Minimal data set / identification of missing data
  - for medical case analysis
  - for regulatory reporting
- Seriousness / expectedness
- Data quality / data validity
- Plausibility analysis
  - biologic characteristics of the product / product targeted disease
  - temporal association
  - underlying disease(s)
  - concomitant medication
- Causality analysis (“can it – will it – did it”)
  - „ADR „diagnosis“ (case definition)
  - differential diagnosis
  - algorithm for causality assessment
- “Narrative”, pharmacovigilance comments
  - objective commenting summary of the case

Case management
Formal and content aspects



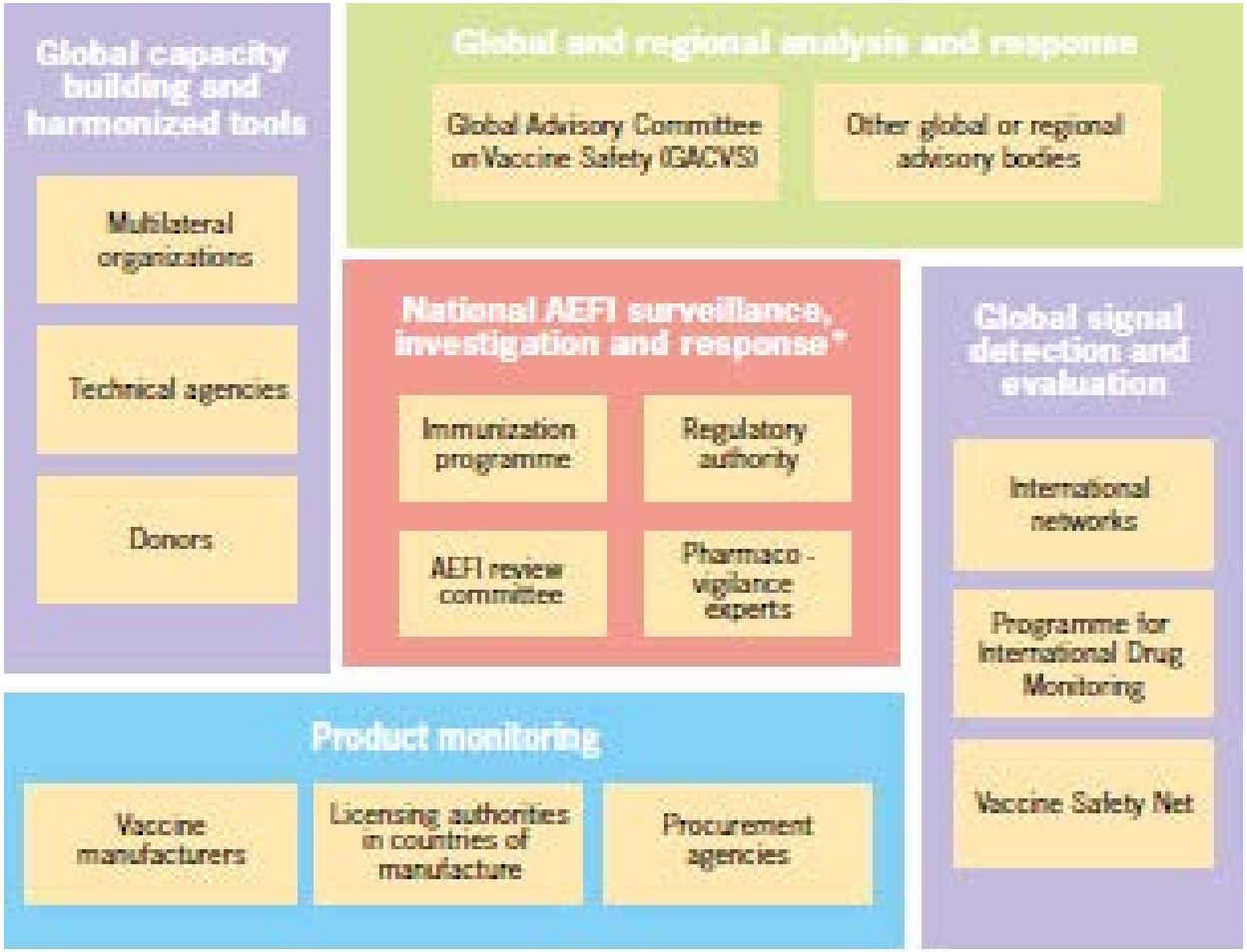
Pharmacovigilance Responsibilities
Depending on status of licensure

Market Authorization Holder (MAH) is legally responsible for Pharmacovigilance



Parties in Global Vaccine Safety

Regional and international awareness and collaboration



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.

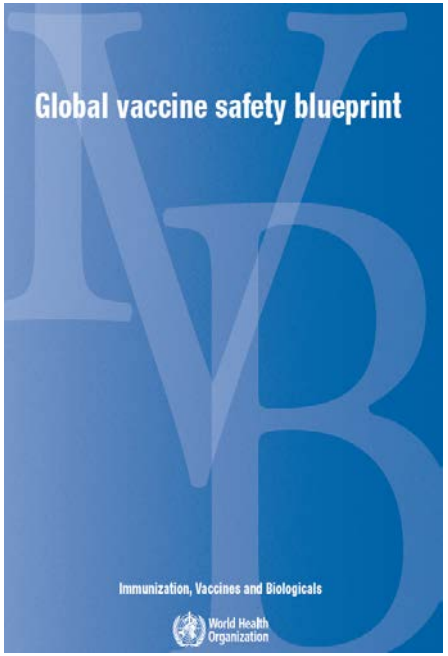
Strategic Goals

- 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.

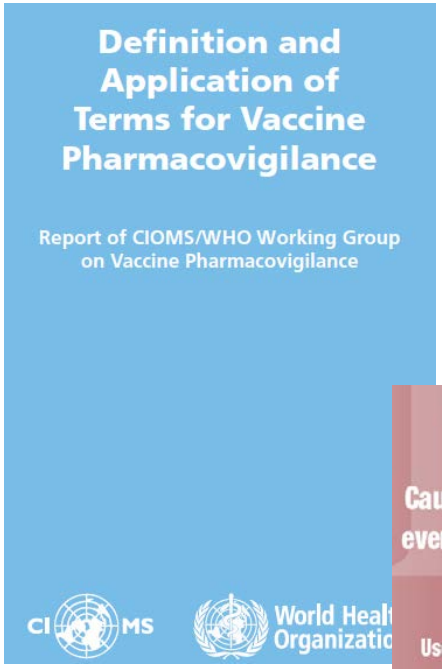
WHO Global Vaccine Safety Blueprint

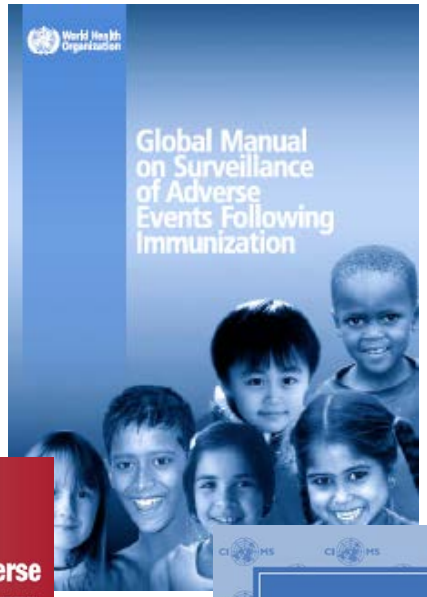
Relationship with industry

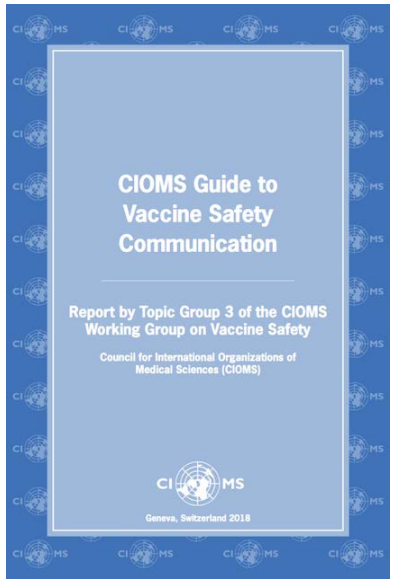
Representatives from vaccine-manufacturer organizations are contributors to the implementation of the Global Vaccine Safety Initiative. In addition, there is an expectation that systems will be established to facilitate interaction between national governments, multilateral agencies and manufacturers. CIOMS is an international, nongovernmental, nonprofit organization which was established jointly by WHO and UNESCO in 1949. Its main objectives are: to facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary; to maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO, and to serve the scientific interests of the international biomedical community in general.[54] Because of its unique position, CIOMS, with assistance from involved stakeholders, is to provide a forum for discussion and exchanges between regulators, national representatives and industry, in order to further the global targets described in Objective 8.

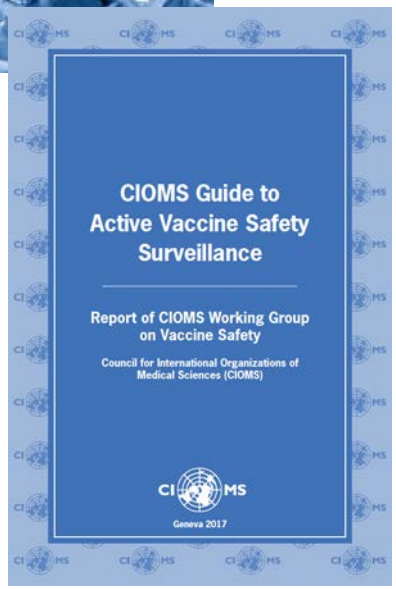


WHO and CIOMS









Vaccine Safety - Points to consider

- Data on AEFIs or on vaccine reactions often do not justify the importance attracted to them in terms of causal validity, or importance compared to disease cases prevented.
- Actively searched AEFIs with little relevance to the background risk ("stamp collections") should not be taken as evidence to support an association:
  - "stamp collections" are vulnerable to post hoc hypothesis generation, however, may form the basis of a hypothesis to be tested by a properly designed study.
- Purported vaccine reactions should be adequately tested for evidence of increased risk of an association in immunized versus non-immunized individuals or cohorts.
- Publication is not proof.
- Do not assume that communication will fix the problem without understanding the problem

Reflections on Pharmacovigilance in Industry /1

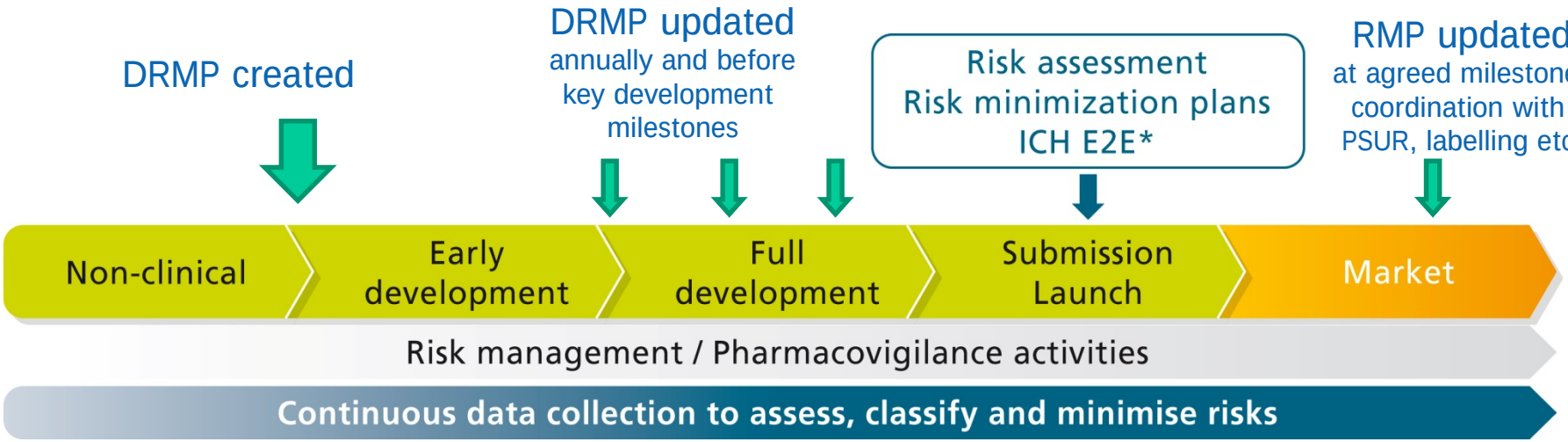
- Companies most often managed by non-medically trained managers:
  - Senior manager's view on vaccine safety can be vague, ill-defined or not understood
- Regulation governing vaccine safety are highly technical and difficult to understand:
  - Managers prefer "Executive Summaries" that may not capture 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 /2

- 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 medicinal product 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

dcvmn
Developing Countries Vaccine Manufacturers Network

More regulations

More processes

More confusion

More inspections

More findings