DCVMN Pharmacovigilance Training
Workshop 15 March 2021

dcvmn
Developing Countries Vaccine Manufacturers Network

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

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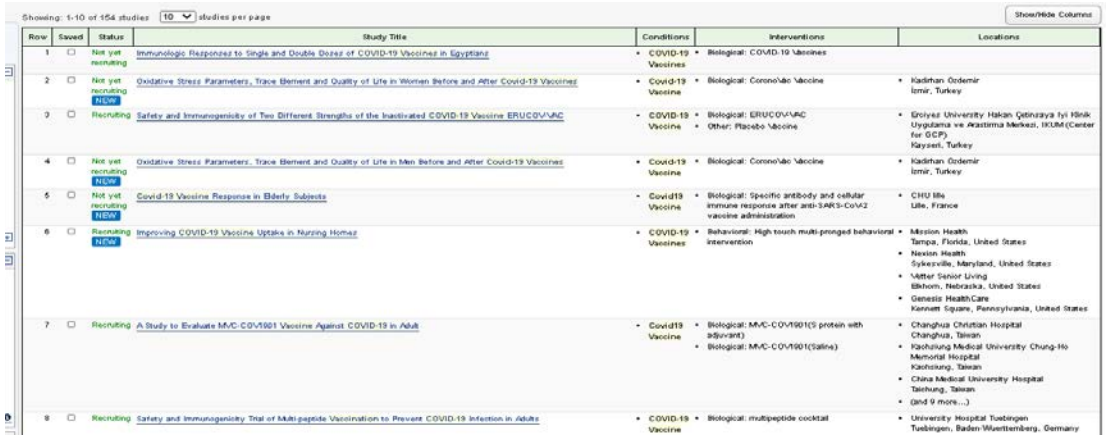
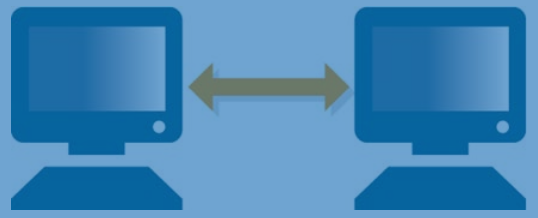
Perception of pharmaceutical industry by the public

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



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 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

Pharmacovigilance is a key responsibility for all vaccine manufacturers

Legally responsible for quality, safety and efficacy

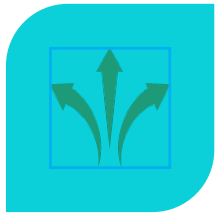
Regulatory requirement and a shared responsibility

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

Requires an appropriate Pharmacovigilance System

Includes all stages of medicinal product development and life cycle

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

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

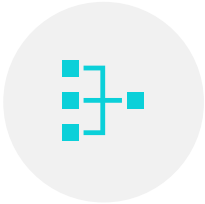
Good Pharmacovigilance Practice

Regulatory requirements

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

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

All persons in the entire organization should engage in continuous improvement



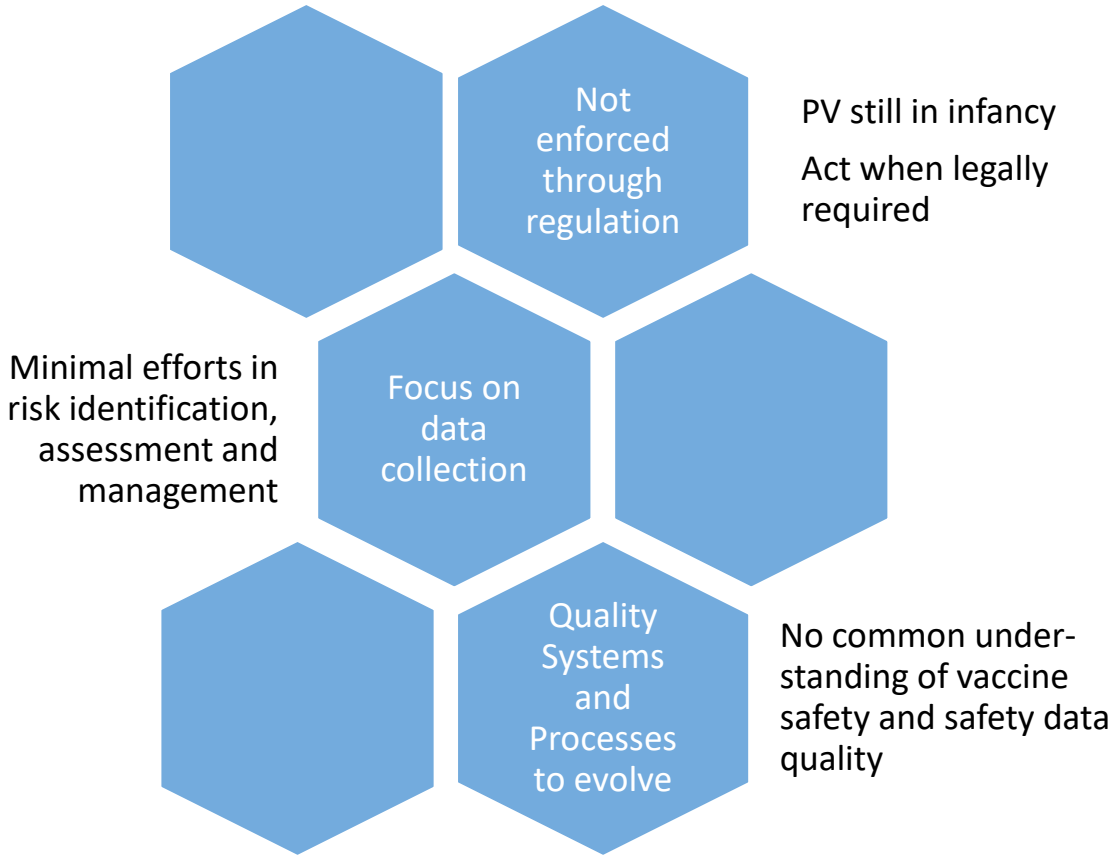
Resources and tasks should be organized as structures and processes to support the proactive, risk-proportionate, continuous and integrated conduct of PV

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

Good cooperation should be fostered between all stakeholders

Good Pharmacovigilance Practice

Current issues in emerging countries



CIOMS Working Group Reports on Pharmacovigilance

CIOMS I: International reporting of adverse drug reactions (final report 1990)

CIOMS II: International reporting of periodic drug-safety update summaries (final report 1992)

CIOMS III: Guidelines for preparing core clinical safety information on drugs (final report 1995 / new proposals 1999)

CIOMS IV: Benefit-risk balance for marketed drugs: evaluating safety signals (final report 1998)

CIOMS V:
Current challenges in pharmacovigilance: pragmatic approaches (final report 2001)

CIOMS VI:
Safety monitoring and evaluation during clinical trials (final report 2005)

CIOMS VII: Development Safety Update Report (final report 2007)

CIOMS VIII:
Signal Detection (final report 2010)

CIOMS IX:
Practical Approaches to Risk Minimisation for Medicinal Products (final report 2014)

CIOMS X:
Evidence Synthesis and Meta-Analysis for Drug Safety (final report 2016)

CIOMS SMQ Implementation: Development and Rational use of Standardised MedDRA Queries (SMQs) (2016)

Each report represents a significant milestone in the development of Pharmaco-vigilance 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

Serious	Severe	Adverse event following immunization AEFI	Adverse event AE
Adverse reaction AR	Serious adverse event SAE	Serious adverse reaction SAR	Expected / Unexpected
	Minimum criteria for reporting to regulatory authority	Frequency 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:**
  - Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/E
  - 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
    - Councel Directive 2010/84/EU
  - 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

GVP Modules

GVP PI Vaccines

- **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

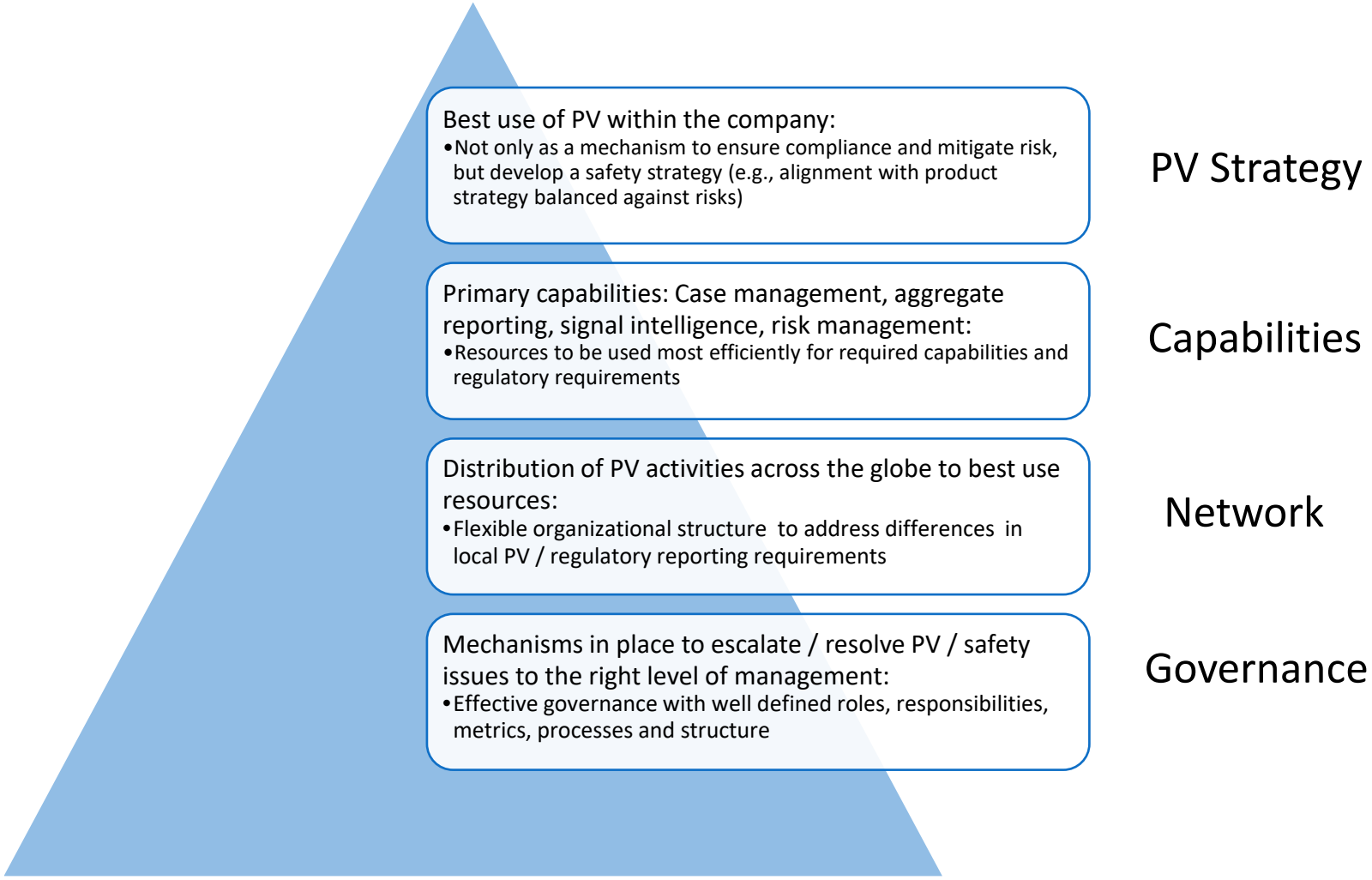
Marketing Authorization Holder (MAH) must ensure that there is an appropriate system in place to assure responsibility and liability for their products world-wide and to ensure that appropriate actions can be taken any time

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

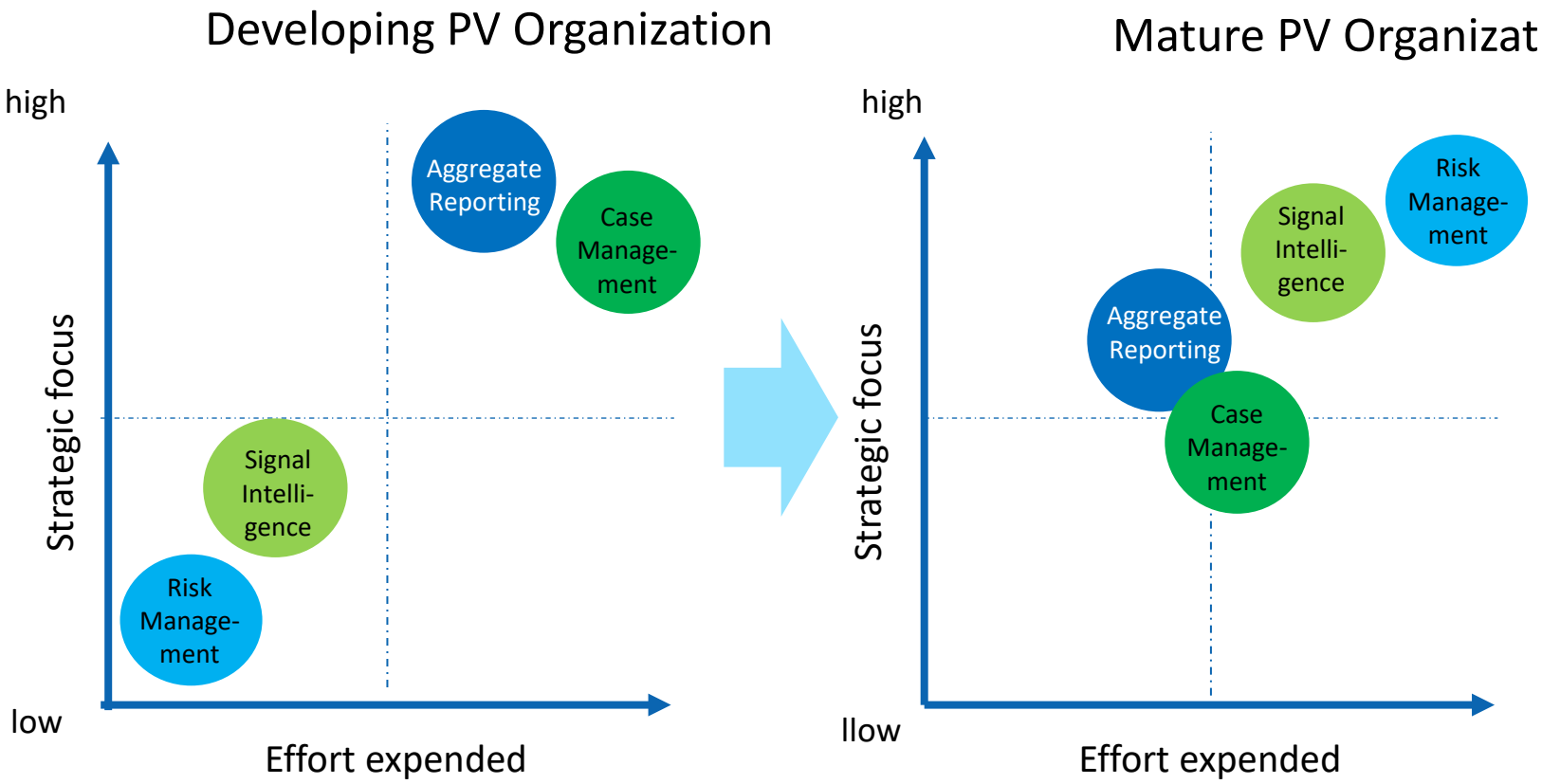
In the EU the QPPV acts as a single point of contact for Health Authorities 24/7 (GVP Module I)

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



Pharmacovigilance activities
Shift from developing to mature PV organization



Deloitte 2011

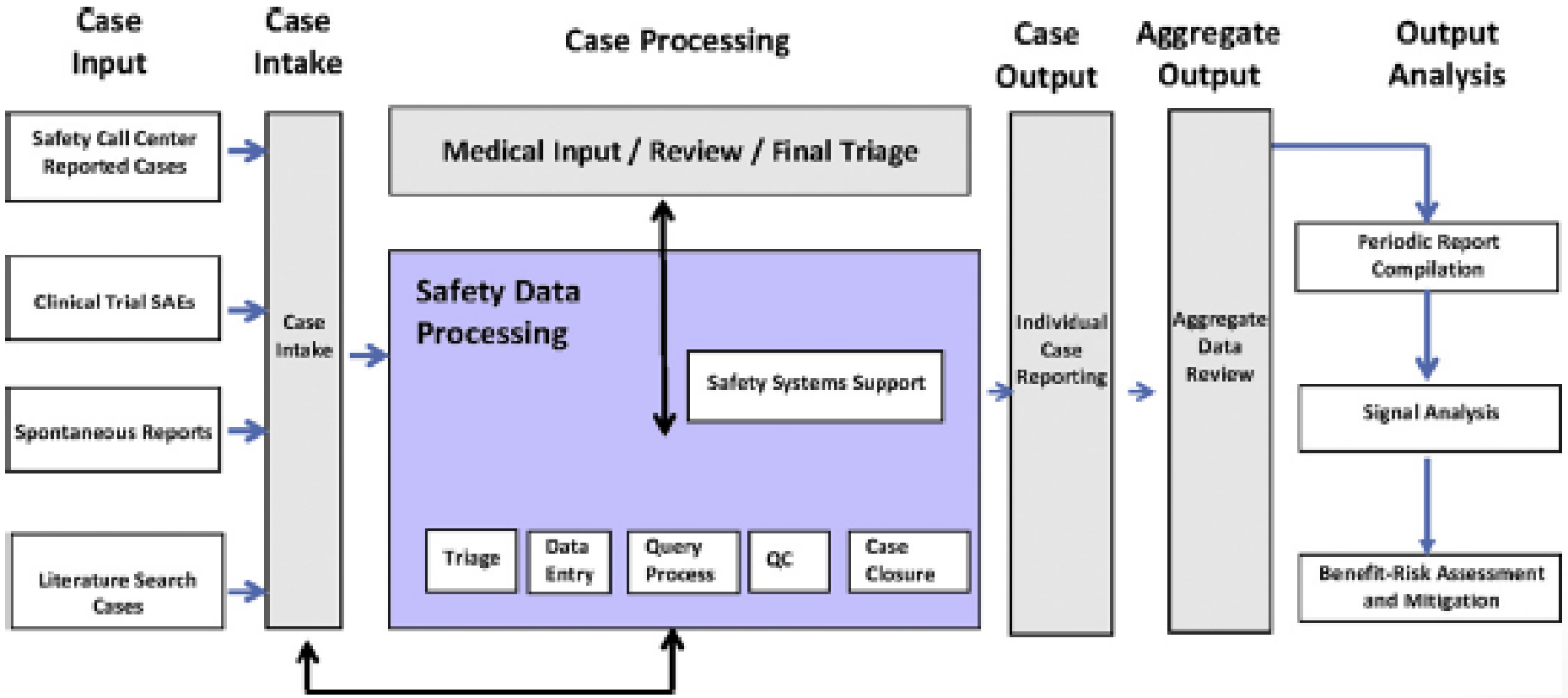
Pharmacovigilance activities
Medical Safety activities in pre- andpost-licensure

Management of all safety matters 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 (e.g., DSURs, PSURs / PBRERs, monthly reports)
	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)

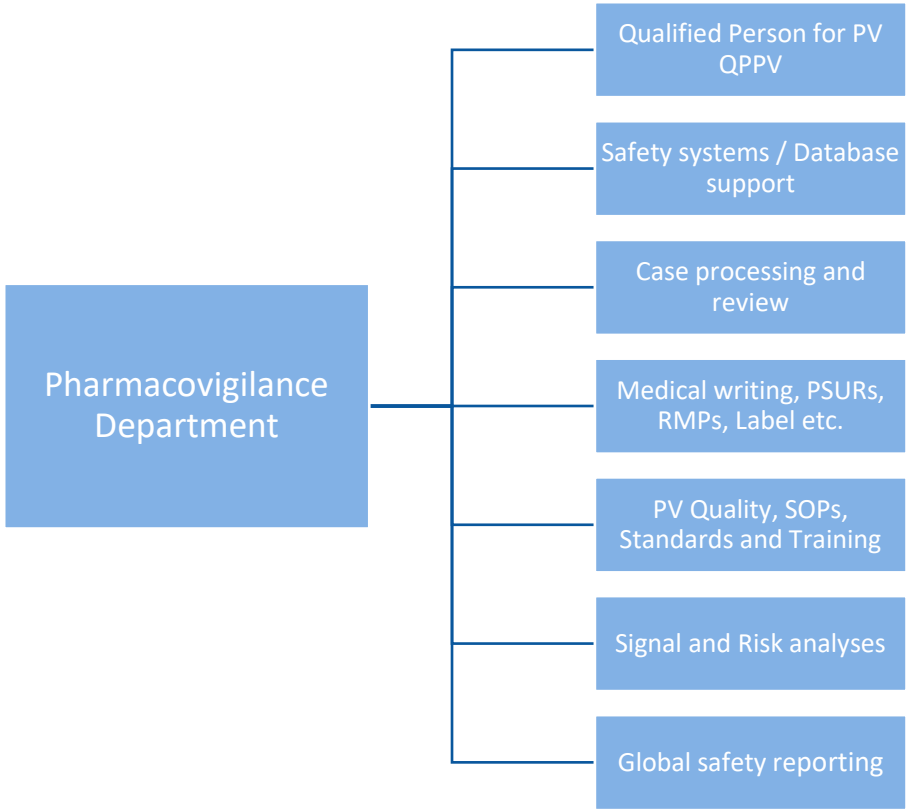
Pharmacovigilance activities
Operational and QA activities

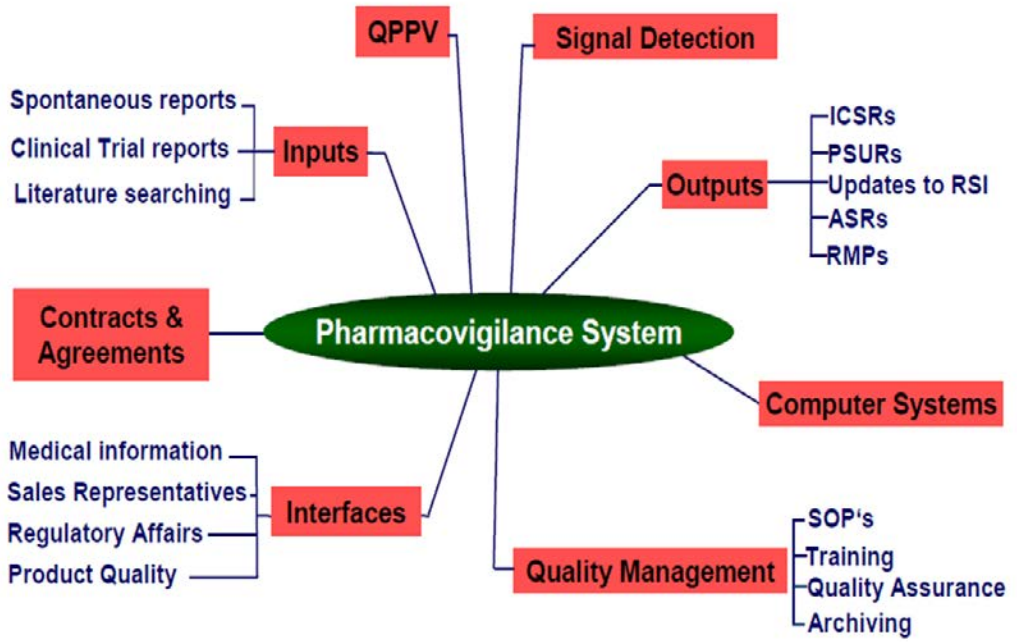
Management of operational / QA (com-pliance) pharmaco-vigilance activities:	Case handling process
	Safety Database
	Regulatory safety compliance
	Regulatory Intelligence
	Compliance management
	PV training: internal / cross functional
	Record management
	Monitoring performance and effectiveness
	Safety Data Exchange Agreements with third parties
	Audit / Inspection readiness
	Business continuation
	Crisis management / Preparedness planning

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 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

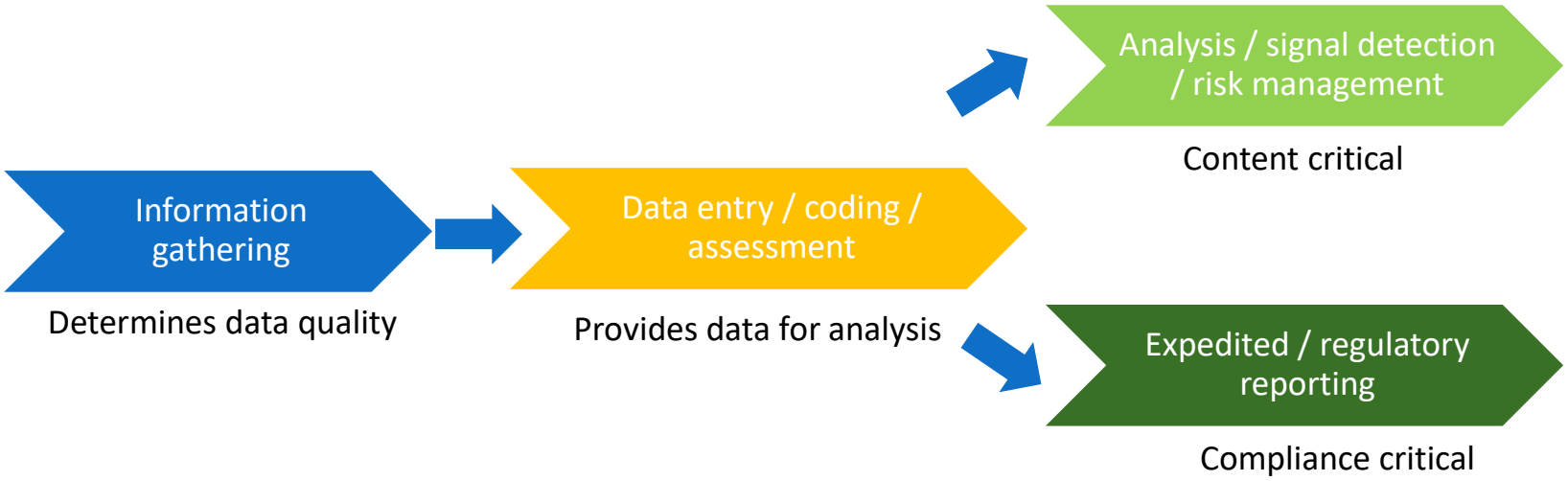
Post-marketing Surveillance Studies (Phase IV; PASS, LSST)

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

Registries

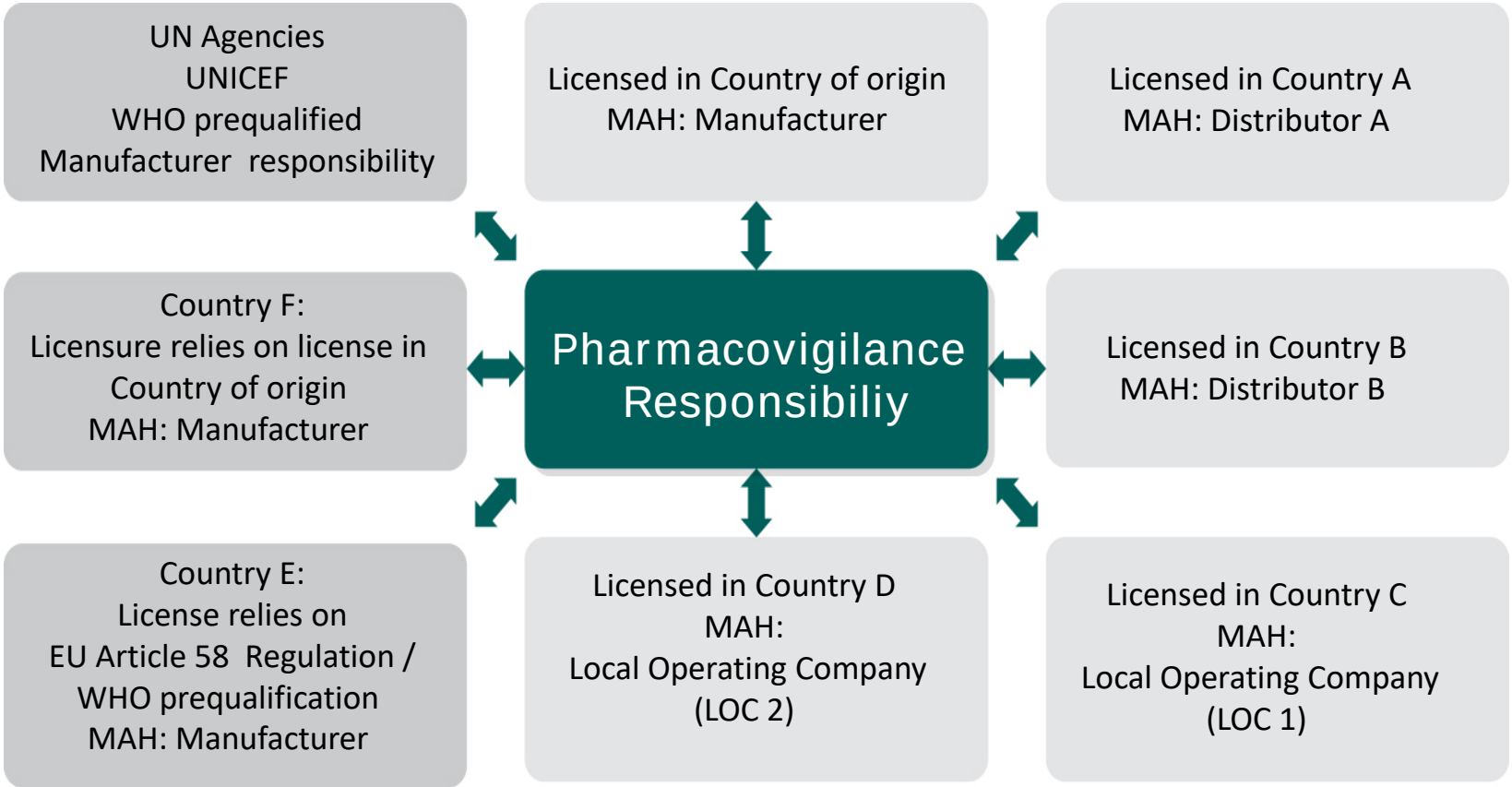
Literature Publications

Case management
Formal and content aspects



Pharmacovigilance Responsibilities
Depending on status of licensure

Market Authorization Holder (MAH) is legally responsible for Pharmacovigilance



WHO / CIOMS Vaccine Pharmacovigilance Guidance

CIOMS / WHO Working Group Reports on Vaccine Pharmacovigilance

- Definition and Application of Terms for Vaccine Pharmacovigilance (2012)

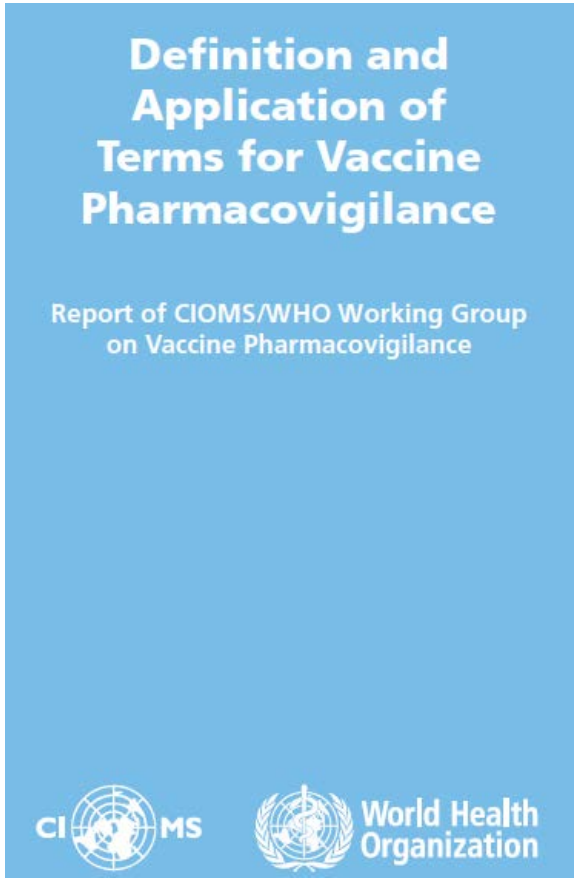
- CIOMS Guide to Active Vaccine Safety Surveillance (2017)

- CIOMS Guide to Vaccine Safety Communication (2018)

CIOMS / WHO Working Group on Vaccine Pharmacovigilance

CIOMS: Council for International Organizations of Medical Sciences

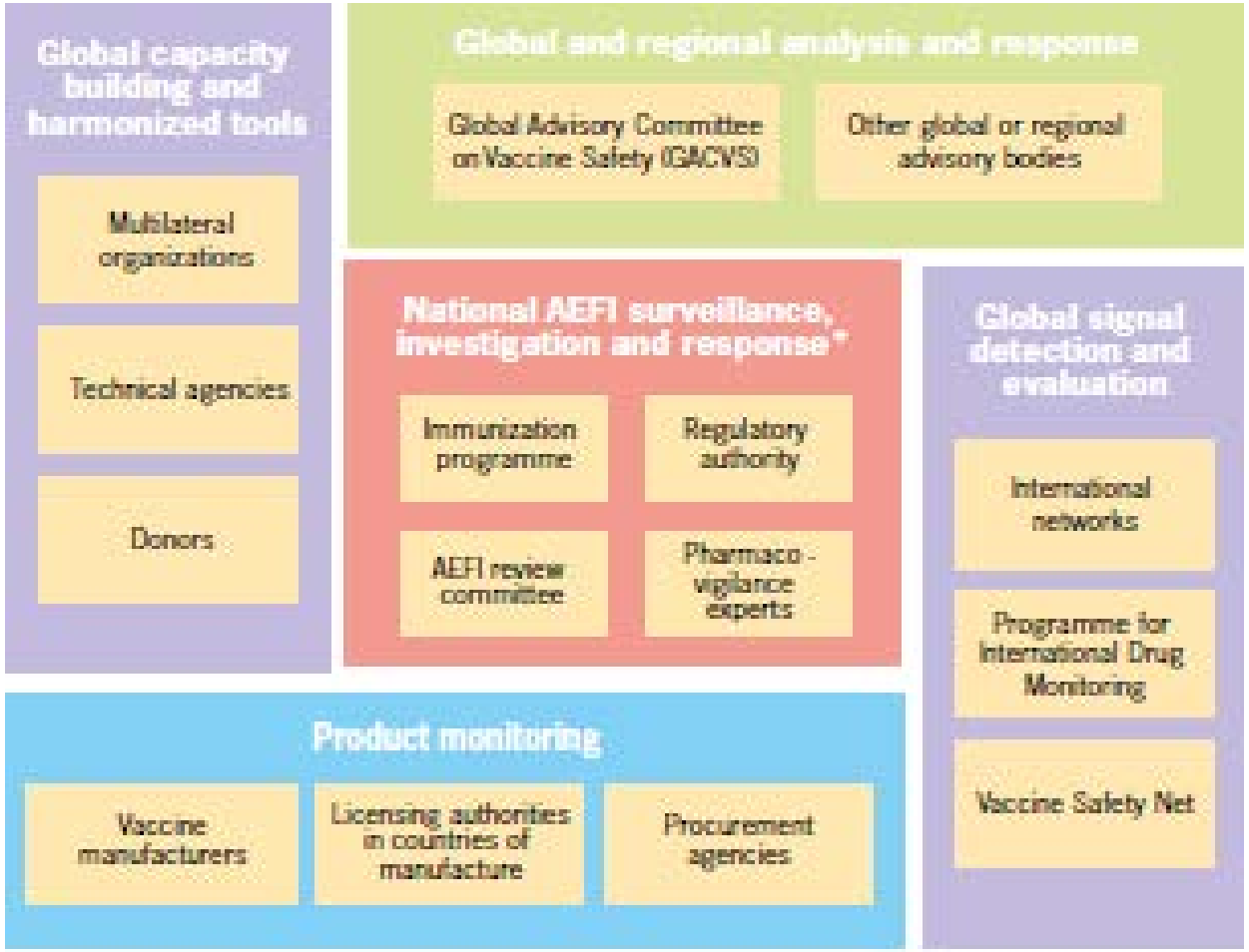
To propose	• standardization of definitions to monitor vaccine safety pre- and post-licensure
To contribute	• to the development, review and approval of AEFI case definitions Brighton case definitions to the dissemination and use of AEFI case definitions
To collaborate	• With other CIOMS working groups WG): ✓MedDRA WG ✓CIOMS WG VIII on Signal Detection relevant to vaccine safety



Parties in Global Vaccine Safety

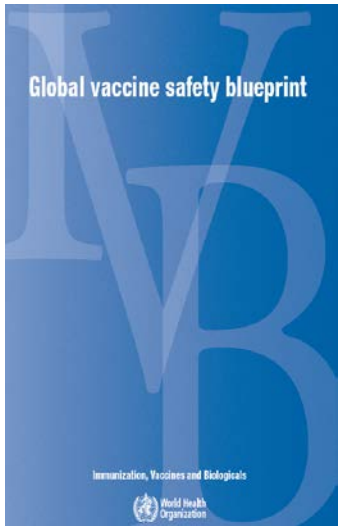
Regional and international awareness and collaboration

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 /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

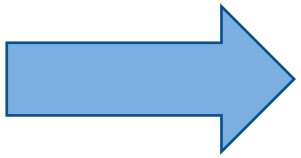
- PV must report into medical research or regulatory departments which are empowered and have organizational voice

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

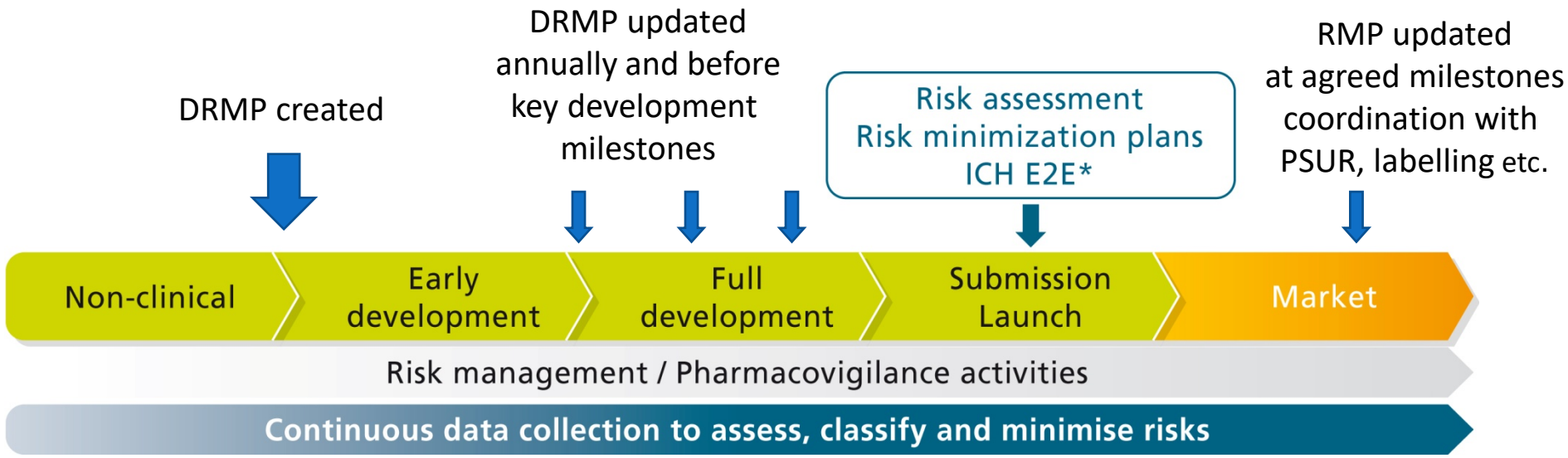
Management often thinks a serious safety issue must be proven by hard data with clear causality

- 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 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