Monitoring Drug Safety in the Market

Role of Industry

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Drug Safety toward Pharmacovigilance
Definition and Scope

- **WHO definition** (2002)**:** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

- **Pharmacoepidemiology** under the scope of Pharmacovigilance

- **Broad Scope of Pharmacovigilance**
  - Pharmaceuticals: Prescription and Over The Counter (OTC)
  - Biological products e.g. vaccines, recombinant, biosimilar etc..
  - Herbal and other traditional medicines
  - Medical devices
  - Cosmetic products

Pharmacovigilance

Stakeholders

- **Patients/Users** increasingly empowered sharing individual experience in a pair to pair manner on the Internet
- **Health Care Professionals** (HCPs)
  - Prescribe the products. Responsible for individual patients
- **Health Authorities**
  - Approve products. Responsible for public health
- **Health Care Industry**
  - Need to innovate to sustain profits, otherwise disappear
- **Media** who, in addition to their mission to inform, may trigger *media issues* to increase their visibility and audience.

Pharmacovigilance in the Industry

Partnering Internally and Externally

- Partnering across functions and with external stakeholder is critical for Industry's PV departments.

Within License Holder's Organisation

- **Regulatory affairs**: Safety communication with Health Authorities
- **Clinical Operations**: Interventional studies
- **Medical Affairs**: Non-interventional studies, Medical Information
- **Commercial functions**: in contact with Prescribers
- **Corporate Communication**: dealing with media

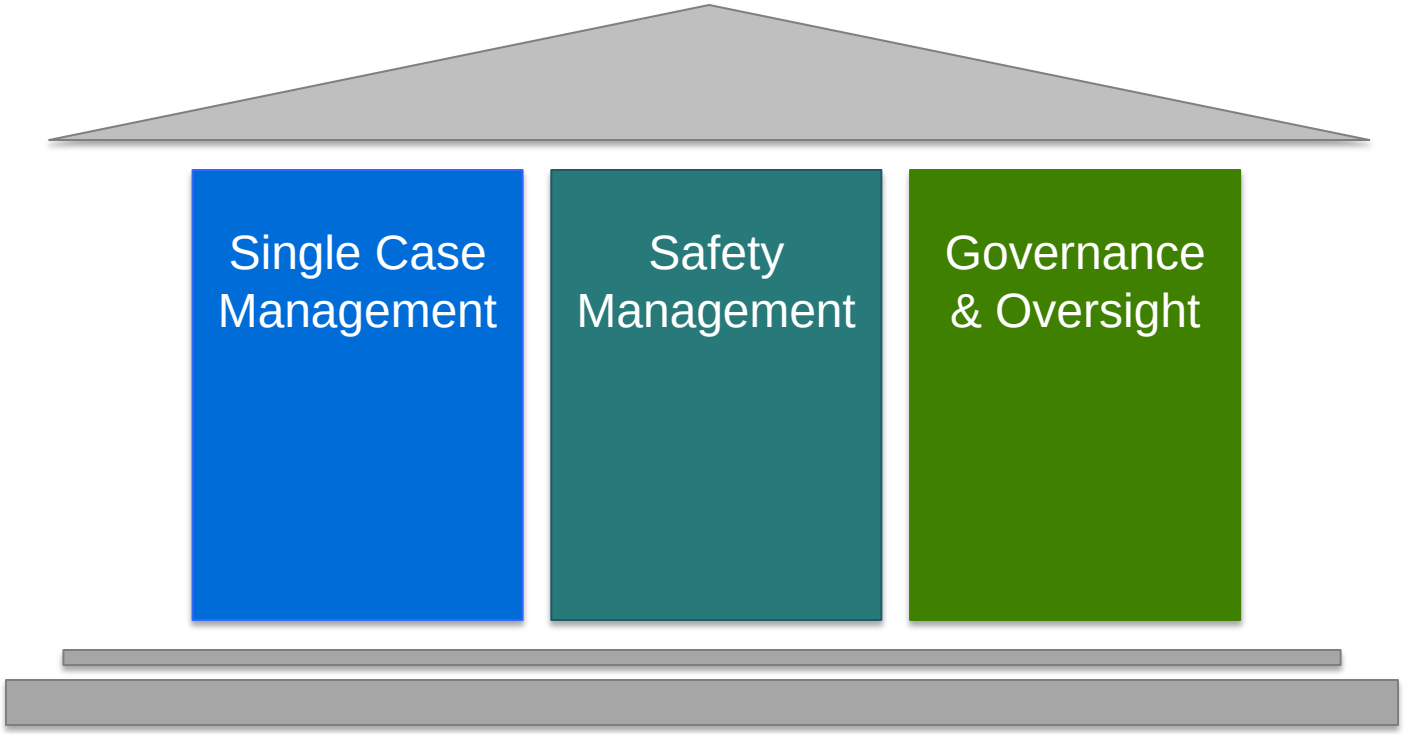
External

- **Health Authorities:** Adverse Events submission, Legislations
- **Academic Experts**: Investigators, Data Monitoring Safety Boards
- **Contract Research Organisations**: Multiple types of investigations

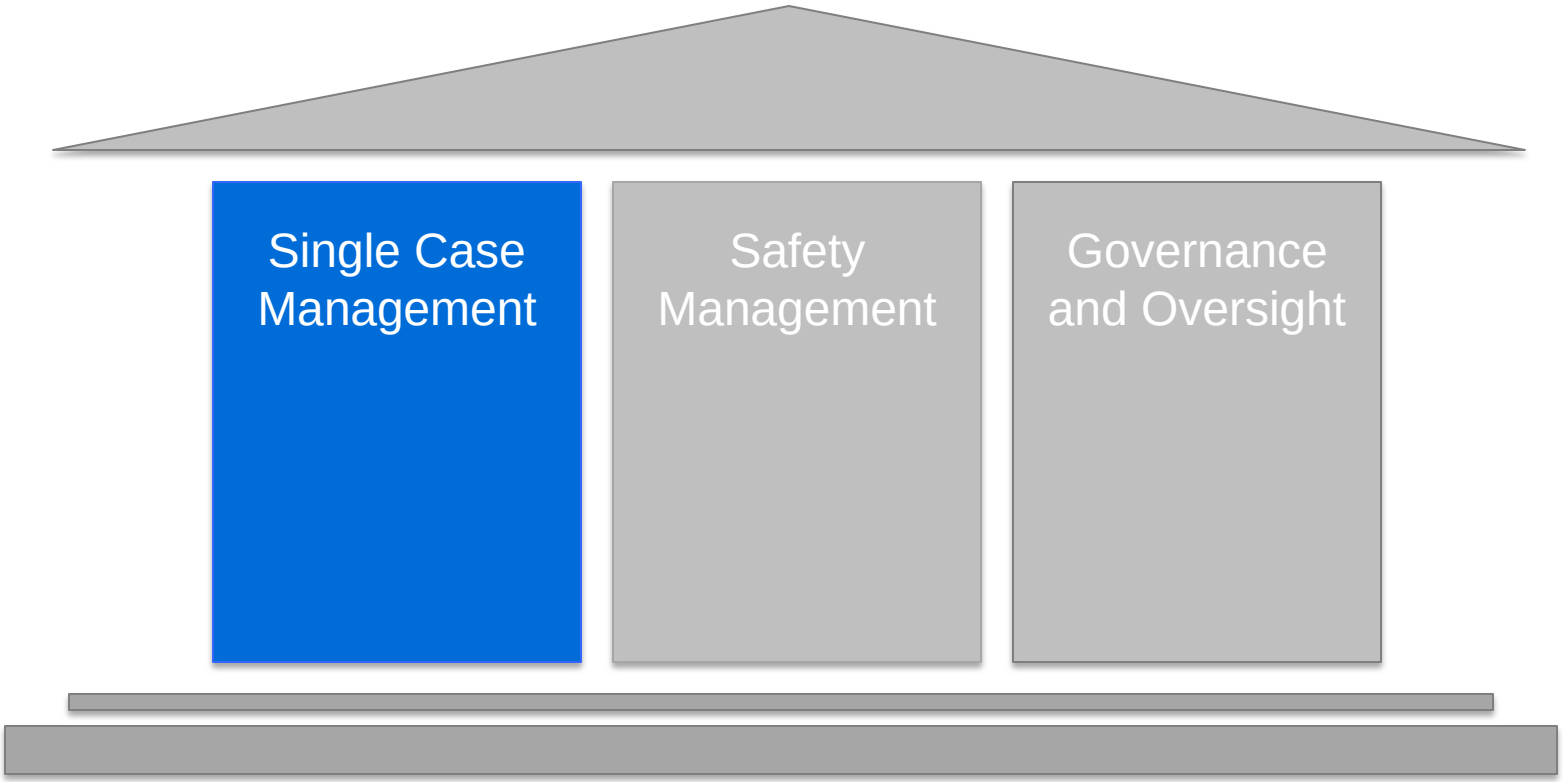
Pharmacovigilance in the industry

The 3 pillars of a broad scope activity

Goal: Maximise the benefit of medicinal products versus the risks, by ensuring the proper use in the approved indications, and minimising the risk of occurrence and impact of untoward effects.



Single Case Management



Single Case Management
Guidelines and Legislations

- CIOMS Group I on *International Reporting of Adverse Drug Reactions* released the CIOMS-1 Report and the CIOMS-1 Form in 1990.
- This work served as basis for the ICH-E2A guideline on *Definitions and Standards for Expedited Reporting* and ICH E2B guideline on *Electronic submission* of ICSRs.
- Those ICH Guidelines were implemented into the Legislations of ICH Countries i.e. USA, EU, Japan, Canada and Switzerland.
- An increasing number of non-ICH countries are progressively aligning their submission requirements with the above guideline. However, complete global harmonization is not achieved.
- Increased stringency resulting from EU-GVP (2012)

Collecting Adverse Events

The *fuel* of Pharmacovigilance activities

Definition of an Adverse Event:

Any undesirable occurrence in a patient or subject receiving a medicinal product, which occurrence does not necessarily implies a causal relationship to the product administered.

- At least one **Adverse Event**
- For an **identifiable** medicinal **product**
- In an **identifiable patient**
- Reported by an **identifiable person**

→ **I**ndividual **C**ase **S**afety **R**eport (ICSR)

ICSR basic Criteria

How to understand identifiable?

- **At least one Adverse Event:** Not necessarily a medical term. May be a lay expression reported by the Patient or Consumer

- **Identifiable Product:** Awareness of the non-proprietary name is enough even if unsure it is a Company product. Details on the formulation and dosage are not required for considering the product identifiable.

- **Identifiable Patient:** Awareness of initials or gender, or age is enough to consider the patient identifiable.

- **Identifiable Reporter:** Information such as "*reported by the consumer himself*" or *"a relative of the patient"*, or *"the treating physician of the patient" or "the pharmacist who delivered the product"* is enough to consider the Reporter as identifiable.

ICSR data collection

Content of CIOMS-1 Form

- Patient initials
- Country of reporting
- Date of birth / age
- Gender
- Reaction onset date
- Seriousness criteria
- Narrative description of the event

- Suspect drug
- Daily dose. Route of administration
- Indication for use
- Therapy dates and duration
- If AE abated or not after stopping drug?
- If AE reappeared or not after re-introduction?

- Concomitant drugs. Date of administration
- Other relevant medical history

- Identification of the Product License Holder
- Source of report: study/HCP/HA/Literature
- Date the report was received
- Report submission date. Initial/Follow-up

CIOMS FORM
SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1.PATIENT INITIALS (first, last)	1a COUNTRY	2. DATE OF BIRTH			2a.AGE Years	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	☐ PATIENT DIED
7+13 DESCRIBE REACTION(S) (including relevant tests/laboratory data)										☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTANCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING ☐ CONGENITAL ABNORMALITIES ☐ OTHER MEDICALLY IMPORTANT

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name and batch no.)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

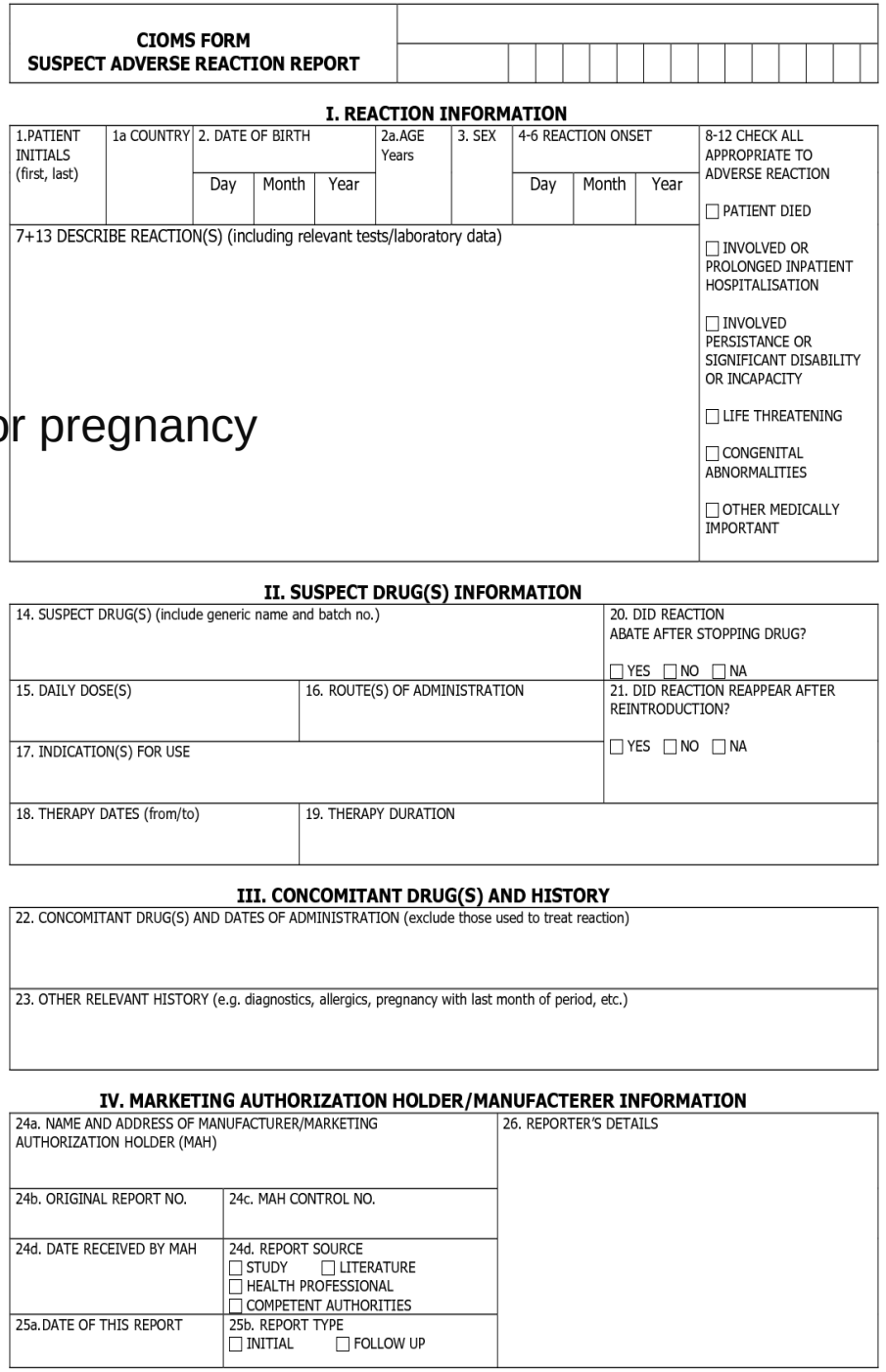
IV. MARKETING AUTHORIZATION HOLDER/MANUFACTERER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER (MAH)		26. REPORTER'S DETAILS
24b. ORIGINAL REPORT NO.	24c. MAH CONTROL NO.	
24d. DATE RECEIVED BY MAH	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ COMPETENT AUTHORITIES	
25a.DATE OF THIS REPORT	25b. REPORT TYPE ☐ INITIAL ☐ FOLLOW UP	

Extended ICSR Scope

Should be handled as ICRS

- Exposure of a pregnant women
- Exposure of the male responsible for pregnancy
- Lack of drug effect
- Overdose
- **Misuse**
- **Medication error**
- **Off-label use**
- **Occupational exposure**
- Product Technical Complaints



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ICSR Handling Process

Reporting Timelines for post-marketing reports

- **Early notification of Deaths:** within 1 day (China, Thailand)

- **7-day AE Report:** Deaths or life-threatening events
- **15-day AE Reports:** Other Serious Events
- **30-day AE Reports:** Non-serious Event (for spontaneous reports)

According to ICH timelines

Most Counties but not all, accept ICH timelines for ICSR submission

Most non-ICH countries request only Domestic ICSRs

ICSR Handling Process
Product Technical Complaints (PTC)

- Product defect classified based upon the nature of the complaint and the potential risk to consumer safety

Category I: Defect potentially life-threatening or could cause serious risk

Category II: Defect could cause illness or mistreatment but not category I

Category III: Defect may not pose a significant hazard to health

Category IV: Defect does not pose a hazard to health

Category V: Non-defective product

ICSR Handling Process

Incidents reported with Medical Devices

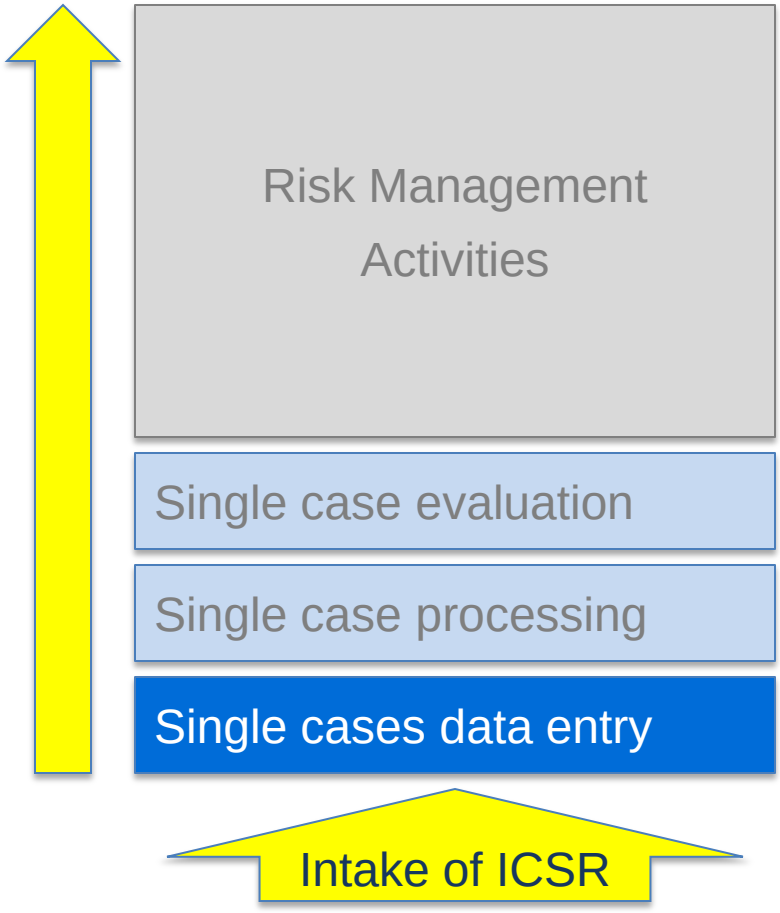
- EU's MEDDEV serving as reference in an increasing number of countries
- Also reported as Product Technical Complaints (PTC)
- Product not necessarily defective

Meeting MEDDEV definition of Incidents

- **2-day Incident Reports:** Serious Public Health Threat
- **10-day Incident Reports:** Serious Event actually occurred
- **30-day Incident Reports:** PTC which may have caused a Serious Event

- **Non-Incident:** PTC associated with a non-serious Event
- **Non-Incident:** PTC not associated with any event

Single Case Management
ICSR Intake and Data Entry

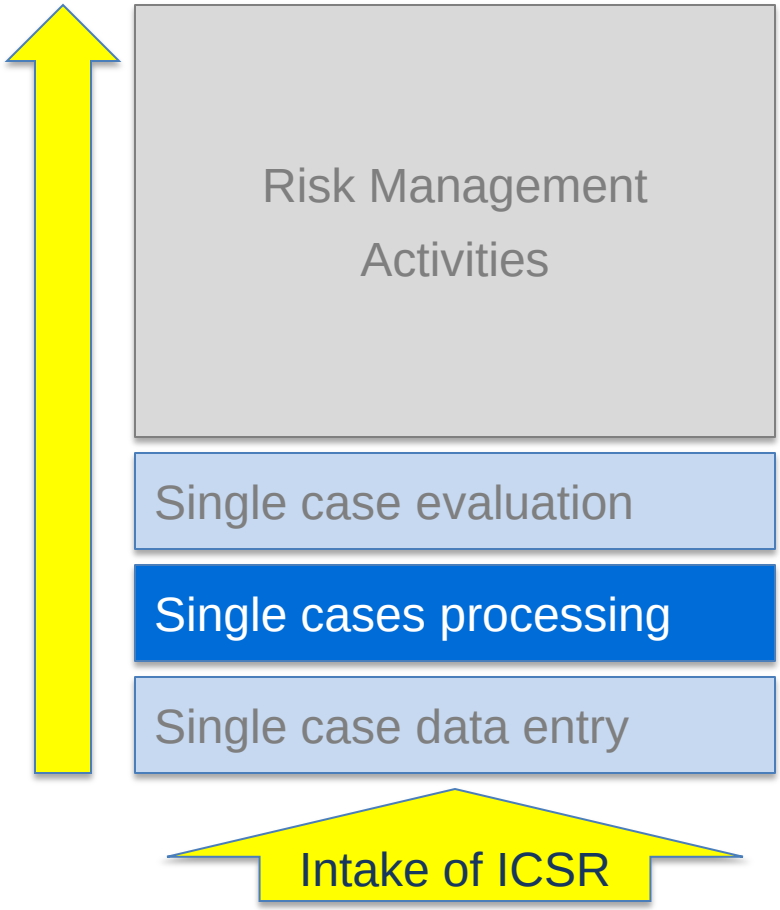


- ❑ Triage, duplicate check
- ❑ Case documentation
- ❑ Translation of source documents
- ❑ Primary data Entry into safety DB
- ❑ Solicited vs Non-solicited

Solicited:
- Interventional and non-interventional studies
- Patient Support Programs
- Market Research and Active Online listening
- Company-sponsored social media
- Product hotlines

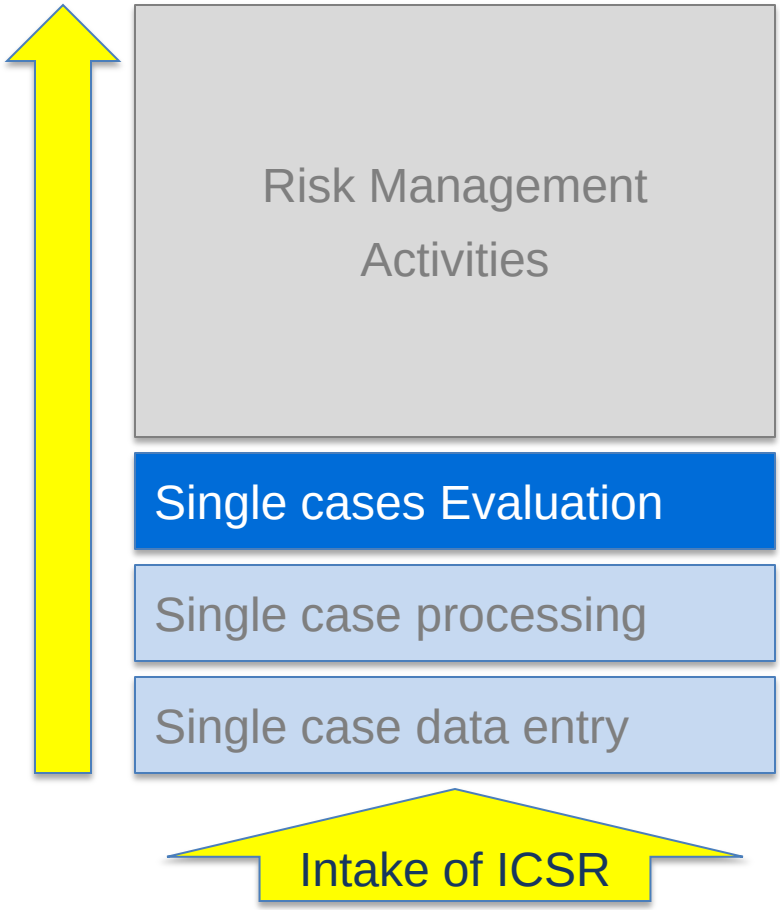
Non-solicited:
- Spontaneous
- Literature

Single Case Management
Processing ICSRs



- **Processing**: information is further structured according to standard rules.
- **Listedness** is established referring to CCDS or Country labeling
- **Seriousness** is checked. Upgrading to serious may be decided
- **Follow-up** information may be requested as a query sent to the reporter.

Single Case Management
Evaluating ICSRs



- **Seriousness** is confirmed
- **Determination of the causal relationship** between the suspected product and the reported event.

- Usually performed by a Medical Doctor centrally
- Country-specific evaluation may be required e.g. Japan, China, France

Evaluating ICSR
Key terminology

- Seriousness
- Causality
- Adverse Event (AE) vs Adverse Drug Reaction (ADR)
- Suspected Unexpected Serious ADR (SUSAR)

Evaluating ICSR
Seriousness

- ***Seriousness*** differs from ***Severity***
- ***Serious AE*** has a safety regulatory definition: AE meeting at least one of the following:
  - Leads to death
  - Life threatening
  - Requires hospitalization/prolongation of hospitalization
  - Results in persistent or significant disability
  - Congenital abnormality or birth defect
  - ***"Medically Important"*** is a more subjective concept

Evaluating ICSR
Seriousness

Medically Important

- Reporter considers it serious
- AE term included into a list of terms *Medically Important* by definition e.g. WHO list, EMA list, Company-specific list.
- The Company may decide to upgrade to Serious e.g. in consideration of the severity of the symptoms.

Remark: Because regulatory submission timelines depend upon the Seriousness, it is safer, in case of doubt, to upgrade the case to Serious in order to ensure case processing according to shorter timelines. Subsequent downgrading (after upgrading) may be possible if justified.

Evaluating ICSR
Causality

- **Adverse event:** Any untoward/undesirable occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily need to have a causal relationship to this treatment.

- **Adverse Drug Reaction:** A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Evaluating ICSR
Causality

Remarks: Different countries may apply different causality categories:

- Definite/Probable/Possible/Unlikely/Not related/Non assessable
- Can/Cannot be denied (with a low threshold in Japan)
- Imputability method (France)

- ***Remark:*** Causally Associated Yes/No, based *upon "at least a reasonable possibility"* is the most practical causality assessment method for decision making in clinical trials (e.g. code breaking) and for the management of large amounts of safety data. However, this can hardly reflect complex safety observations.

Evaluating ICSR
Causality

Important remarks:

- The Reporter and the Company may apply a different Causality assessment for an individual case. Then:
  - The divergence of opinion shall be made very transparent in the ICSR submitted to Health Authorities
- Overall, the most conservative causality assessment shall prevail i
  - Serious shall prevail versus Non-Serious
  - Causally related shall prevail versus Non-related

Evaluating ICSR

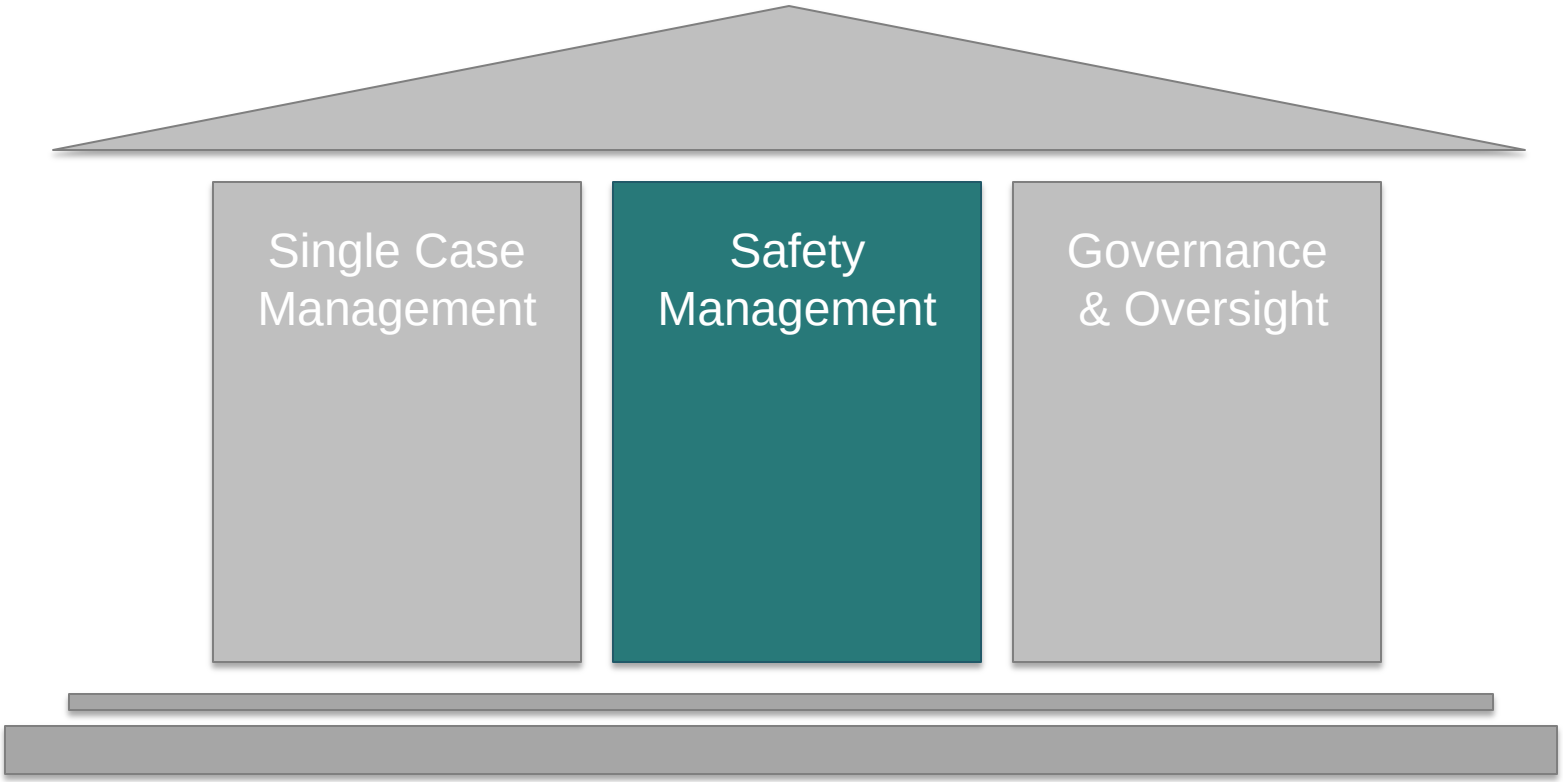
Suspected Unexpected Serious Adverse drug Reactions

- **SUSARs:** Causally-related and Unlisted (unexpected) ICSRs
- Constitute new serious safety information: Expecially under scope
- Should be reported to Investigators and Ethics Committees of clinical trials
- Should be reported blinded or un-blinded depending upon Country / Ethics Committee requirements

Major harmonisation issue

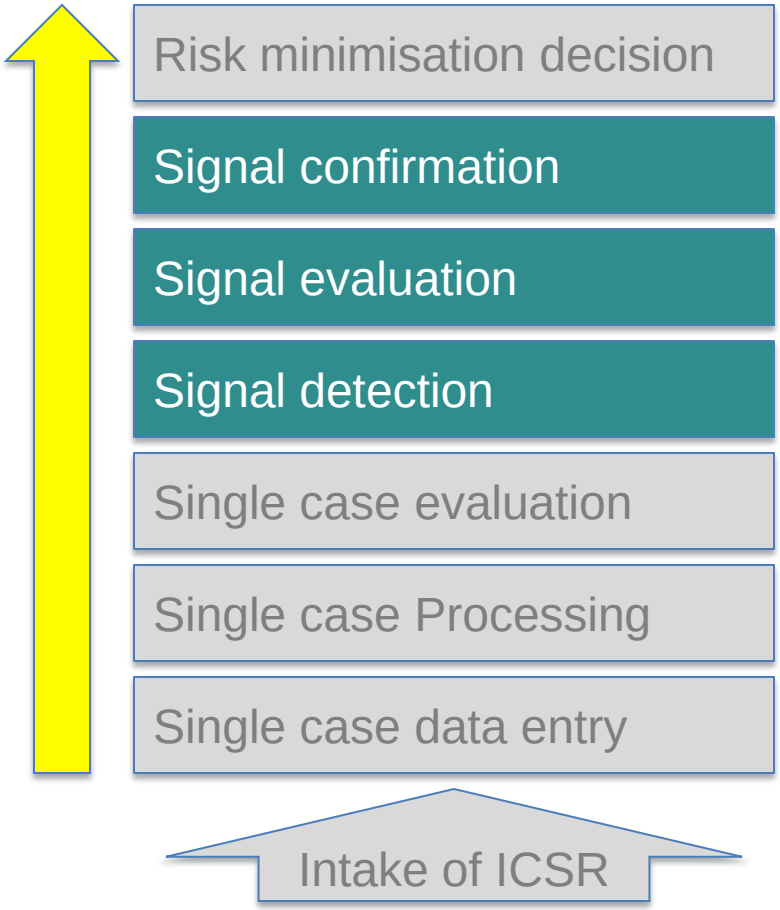
- Rules applicable for submitting SUSAR to Investigators and Ethics Committee, vary depending upon Countries, from a expedited reporting, to summary listing, every 3 to 6 months.

Safety Management



Safety Management overview

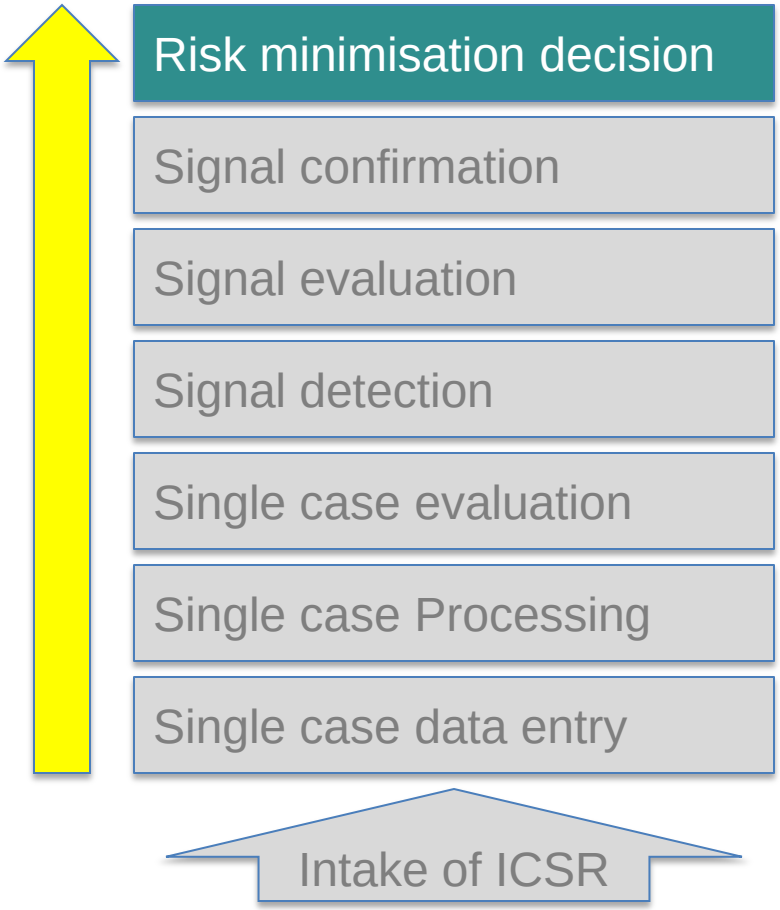
Activities beyond Single Case Management



- Considering further inquiry
- Based upon medical judgment.
- Computerised algorithms in addition standard methods

- Consistently reflected in Risk Management Documents
  - PSUR/PBRER
  - Benefit/Risk Statement
  - Risk Management Plan

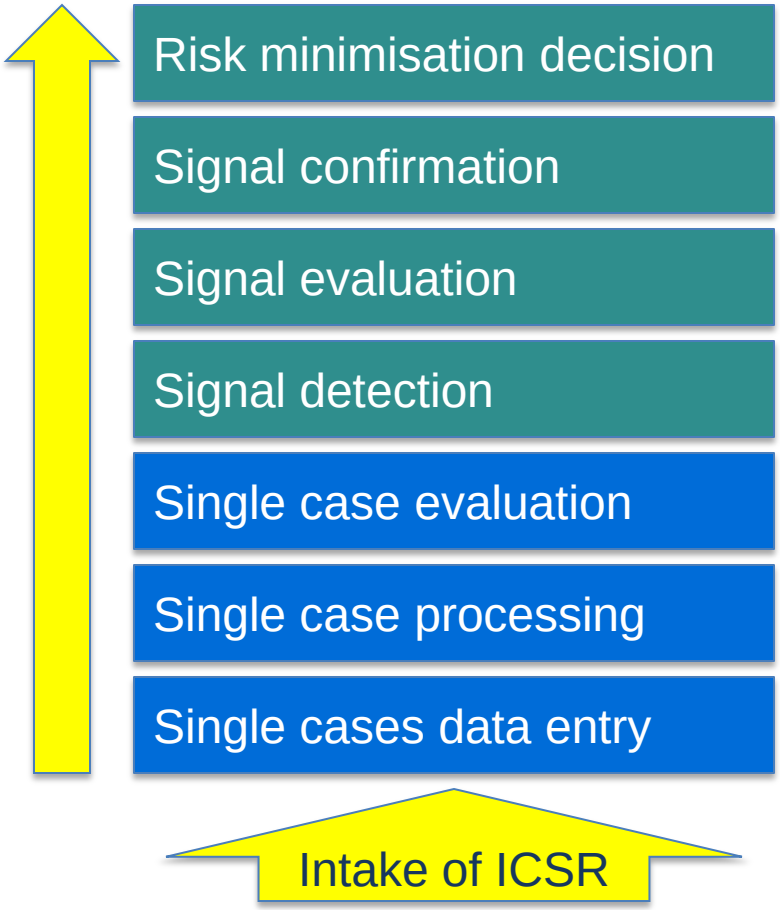
Safety Management overview
Risk Management decisions

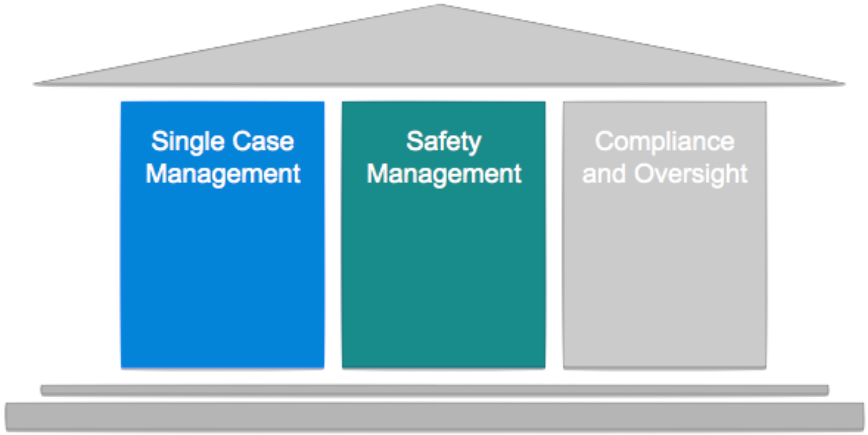


- Following processed under strict medical governance

  - Change in the CCDS of the product
  - Change in the content of the RMP
  - Risk Minimisation decision

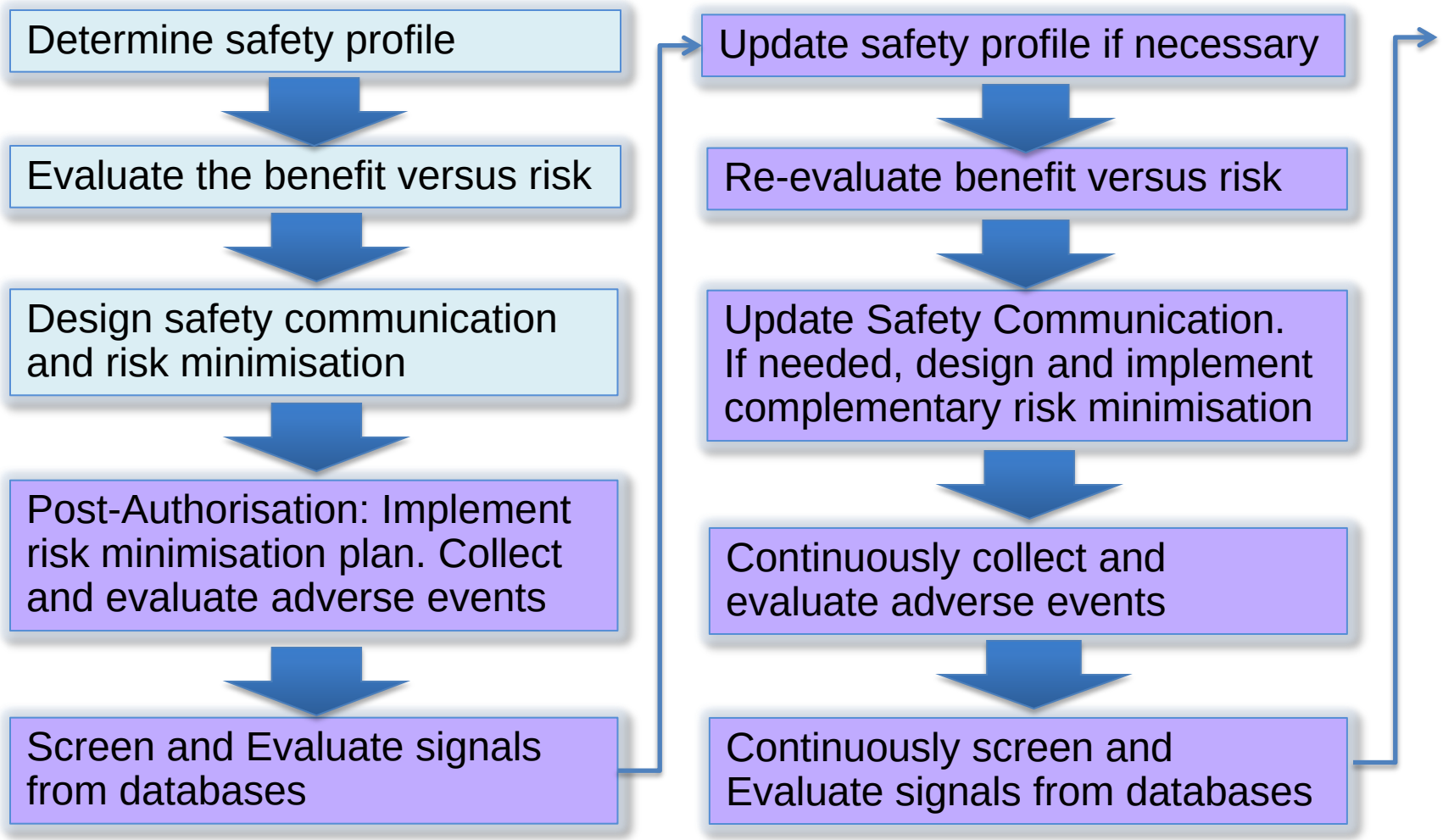
Safety Management overview
Cycles of Risk management Activities





Safety Management overview

Cycles of Risk management Activities



Safety Management Overview
Cycles of Risk management Activities

How to achieve it?

- **Regulatory framework**
- **Methodology**
- **Resources**
- **Processed**
- **Governance**

EU-GVP Module V
Risk Management Systems

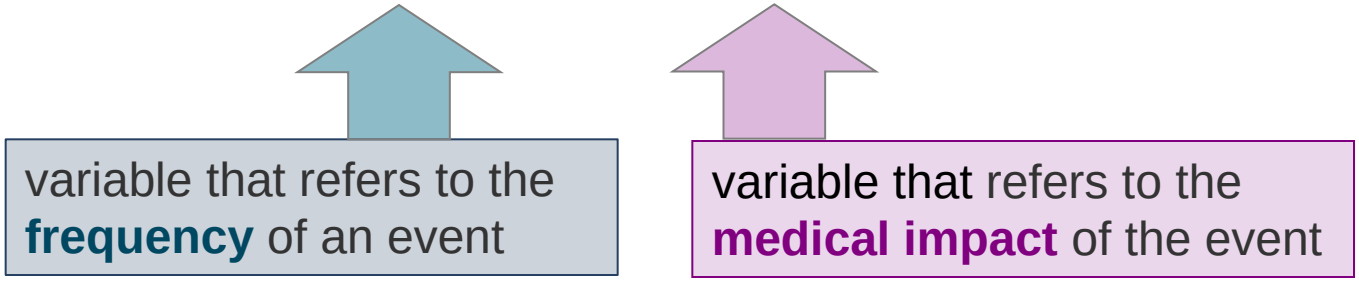
- 2004 / 2005: the ICH-E2E guideline implemented in the EU, USA and Japan PV regulations.

- 2012: **EU-GVP Module V: Risk management systems**
  - **New EU-RMP Template** more complex than in Volume 9A
  - A revision of the EU-RMP template is under discussion.

ICH-E2E & EU-GVP Module V Part II
Safety specification

Key concepts of the ICH-E2E Guideline:

- "**Safety risk**" is the **Probability of harming** as an outcome of product intake
- **Level of Risk** = **Probability of harming** X **Severity**



ICH-E2E & EU-GVP Module V Part II
Safety specification

❑ Identified Risk

- Adequate evidence of an association with the product of interest

❑ Potential Risk

- Some basis to suspect an association with the product. However, the association is not yes considered as confirmed

❑ Important Risk

- Depends upon the seriousness in consideration of the impact on individuals and/or public health
- *Remark*: Risks referred to in the *contraindications* or *warnings and precautions* sections of the CCDS are usually categorised *Important Risks.*

ICH-E2E & EU-GVP Module V Part II

Safety specification

- **Important identified risk**
  - e.g. abnormal liver function test observed during clinical development suggesting a risk of hepatic impact
- **Important potential risks**
  - e.g. no clinical evidence in human so far but histological findings in an organ in one animal species. Or chemical structure has some similarities with a drug known to impact an organ
- **Important missing information**
  - e.g. no experience in a category of patients or medical situation in whom the product may be used after launch.

Safety Management
Core Safety Management Teams

- Chaired by a Global Safety Leader (GSL)
- Product-wise multi-disciplinary team of internal experts
- Responsible throughout the life cycle of the product for ensuring that the benefit versus risks remain positive, otherwise the GSL shall escalate the concern to the next governance level.

➢ **GSL responsible for Risk Management deliverables throughout the whole life cycle of the product** *(next slide)*

Safety Management
Safety Management Documents

- Safety input into the *Project Master Plan*
- **Benefit-Risk Summary** (BRS): scientific evaluation of risk benefit balance and summaries of data relevant to benefits and risks.
- **Benefit Risk Profile** (BRP) concise document with bullets for each benefit, risk, and risk minimization actions.
- **Periodic Safety Update Reports** (DSUR and PSUR) following the ICH E2C (R2) Periodic Benefit Risk Evaluation reports (PBRER) format
- **Risk Management Plan** (RMP)
  - Development RMP (until Phase III)
  - Core RMP (after Phase III throughout life cycle, reflecting Company position)
  - EU-RMP at initial submission to the EMA
  - EU-RMP resulting in EMA approval
  - Local RMPs and REMS in non-EU countries

Safety Management

Benefit vs Risk Assessment (RMP and PBRER)

- **Comprehensive, concise and critical analysis** of the Benefit vs Risk (B/R) balance of the medicinal product

- Incorporating an evaluation of the safety, efficacy and effectiveness information that becomes available (Basis for evaluating B/R balance)

- The **Risk evaluation** should cover all uses of the product including non-approved indications and other uses.

- The **B/R balance** should be evaluated for each indication individually and for each of the populations susceptible of receiving the product.

Remarks

- The strengths, weaknesses, and uncertainties of the evidence used in the B/R evaluation should be discussed.

Safety Management
Local Safety Management Team

Chaired by the Country Pharmacovigilance Head

- **Membership**
  - Country Medical Director
  - Country Pharmacovigilance Head (Lead)
  - Local Regulatory Affairs Head
  - Representatives from other functions as required

- **Responsible for**
  - Adapting the RMP to Country requirements
  - Preparing Country-specific RM documents
  - Addressing country-specific RM requirements
  - Escalating requests from HA to the Global Safety Leader
  - Supervising locally the execution of risk minimization commitments

Safety Management
Processes under Medical Governance

- Scheduled review of the accumulating safety information
- Evaluation of the outcome of computerized signal detection
- Scheduled delivery of Risk Management documents
- Structured process for the review of RM documents
- Structured escalation of Safety Observations and Signals
- Structured safety decision making process

- All processes apply during clinical development and afterwards, throughout the entire life cycle of the product
- All operated under Medical Governance authority

Safety Management
Escalation of Safety Observations

- Structured process for escalating *safety observations* and assess whether they constitute safety signals
  - Safety Decision & Medical Governance Committee
  - ↑ Safety Review Committee
  - ↑ Global Safety Leader / Therapeutic Area Safety Head
  - ↑ Regional PV head / Global Safety Leader
  - ↑ Country Pharmacovigilance Head/ Drug Safety Officers

➢ *More details in the following section (Medical Governance)*

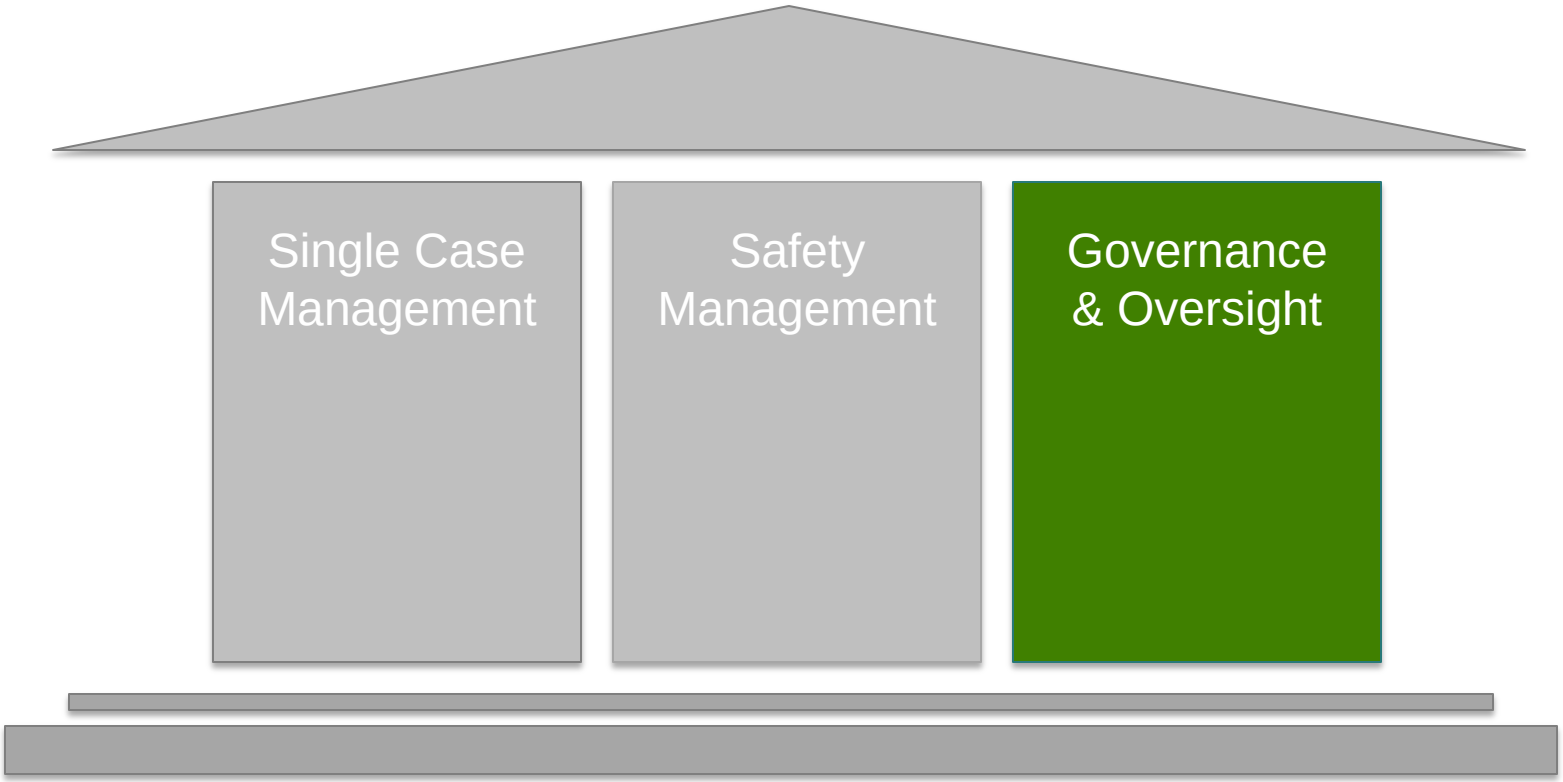
Safety Management
Monitoring Risk Management Commitments

- Risk management commitments are monitored by a dedicated function belonging to Risk Management.

- Ensuring that risk minimization commitment are:
  - Adequately justified (e.g. by Country HA request)
  - Approved by the relevant global medical governance committee
  - Actually and properly implemented and executed
  - and that risk minimisation activities are properly recorded

- Global scope because not only EMA and US-FDA may request additional risk minimisation.

Governance & Oversight



Governance

Escalation to Safety Governance Boards

Governance
Safety Review Committee

- Meet several times a month
- First instance safety board in the escalation process
- Receive and evaluate safety observations
- Request investigations to clarify safety observations
- Evaluate whether a safety observation should be considered as a safety signal and escalated to the Safety Decision & Medical Governance Committee.

Governance
Global Safety Committee

- Meet at least once a month
- Endorses Benefit Risk Statements
- Provide mandatory input at the clinical development milestones
- Endorse/challenge decisions escalated from the SRC
- Approve safety objectives and interventions
- Recommended risk management/minimisation actions
- Supervise the implementation of Risk Minimization measures
- Supervise the execution of the processes under Medical Governance

Oversight
Training on ICSR Reporting obligations

- Any Company employee, has the obligation to report in a timely manner (24h) to the PV department of the Company, any AE associated to the use of a Company product which she/he may become aware of, **including in non-professional circumstances.**

- Applies also to external business partners (e.g. CRO), or contractors (e.g. Academic experts or nurses) **during their contractual activity for the Company.**

Oversight
Contactual Agreements

- **Pharmacovigilance language** embedded into Main Contractual Agreements.

- Separate **Pharmacovigilance Agreements** referred to in the Main Agreement

- **Ensuring that any Medical or Commercial activity involving Patients administered any Company product is under scope**

Oversight
Diverse source of Safety Information

- Health care professionals (HCPs)
- Consumers, Patients, Communities, Associations, Lawyers
- National public health system / Health Authorities
- Interventional and non-interventional clinical studies
- Investigators-sponsored studies
- Numerous types of non-interventional programs
- Market research investigations
- Medical and scientific literature
- Product-dedicated hotlines or social media
- Data mining investigations
- Collection of real life evidence data
- New sources to be invented…

Oversight
Non-Interventional Programs

- Early Post-Marketing Vigilance Phases (Japan)
- Post Marketing Vigilance Program (Indonesia)
- Patients Support and Disease Management Programs (PSDMPs)
- Market Research Studies
- Compensation and Reimbursement Schemes
- Any collection of product use information at the patient level

Important Remarks

- **Any collection of information at the individual patient level may expose to the awareness of information qualifying for an ICSR**

Oversight
Social Media

- **Company-sponsored Websites**, Facebook pages, Twitter etc..
- **Health Authority websites** giving access to ICSR information

- *Are non Company-sponsored social media under scope?*
  - Screening the myriad of non Company-sponsored social media is hardly possible. No regulatory obligation to screen them so far
  - Search engines are being developed to detect ICSRs from the whole Internet possibly detecting amounts of information which can hardly be inquired and medically confirmed.

Oversight
Global Trends in Safety Communication

- ICH and non-ICH Health Authorities make available on the internet an increasing amount of information relative to the safety of medicinal products, including:
  - Anonymised ICSRs
  - Graphs of compiled post-marketing safety information
  - Suspicion and confirmation of safety signals
  - Description of risk minimisation activities.
- Health Authorities interact with each other increasingly across borders

➢ **Pharmacovigilance is performed in a context of global transparency and fast communication.**

Concluding Remarks

- Pharmacovigilance nowadays is the result of 50 years of evolution toward:
  - More sophisticated PV systems
  - More stringent legislations
  - Earlier detection of safety signals
  - Implementation of additional risk minimisation
  - More transparent risk communication

- No longer limited to ICH regions this evolution is spreading globally including in developing countries.

- Further evolution is anticipated as consumers and patients accessing information instantly from anywhere, are getting increasingly sensitised about safety matters, empowered and demanding.

Monitoring Drug Safety in the Market Role of Industry

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Thank you for your attention

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