Pharmacovigilance Practice in Pharmaceutical Industry

From Adverse Event Collection ➔ Risk Management

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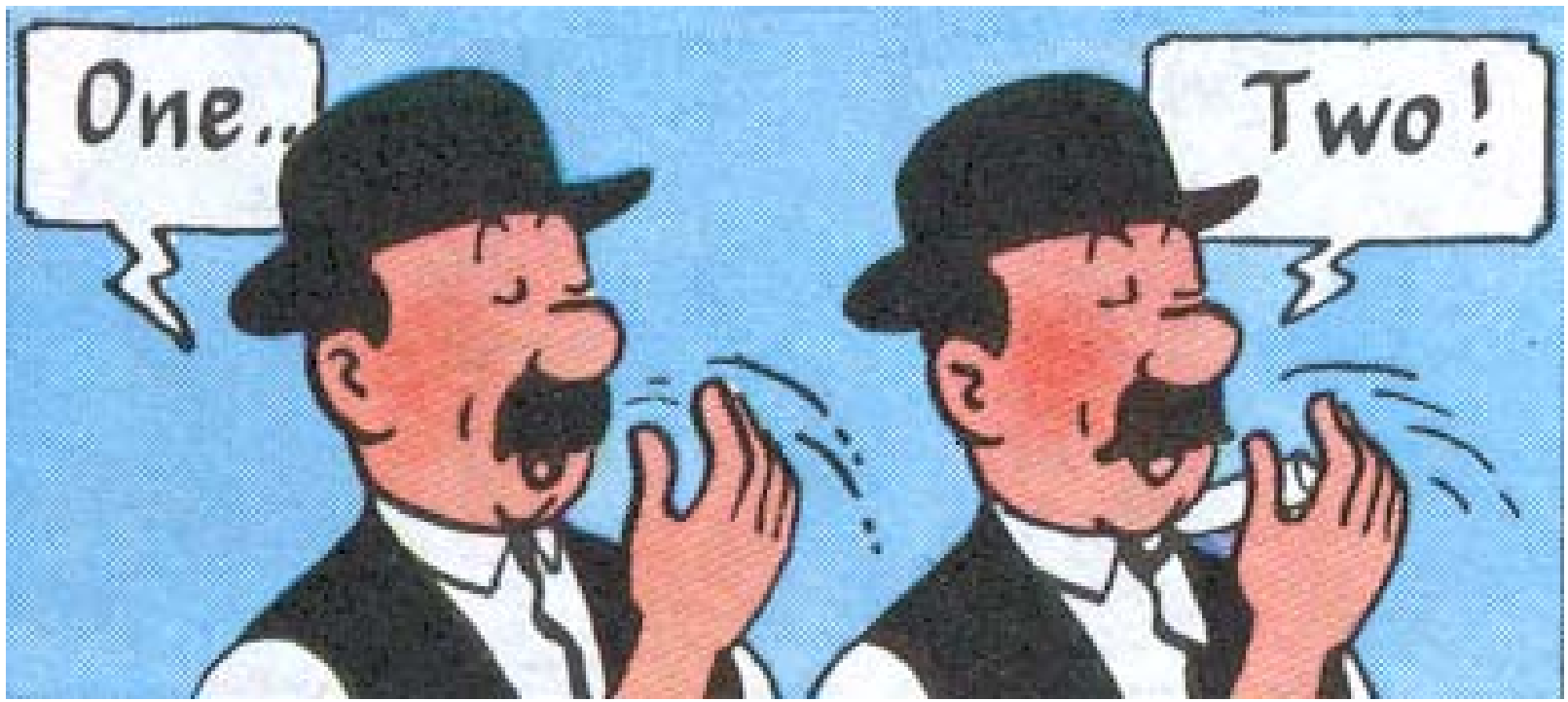
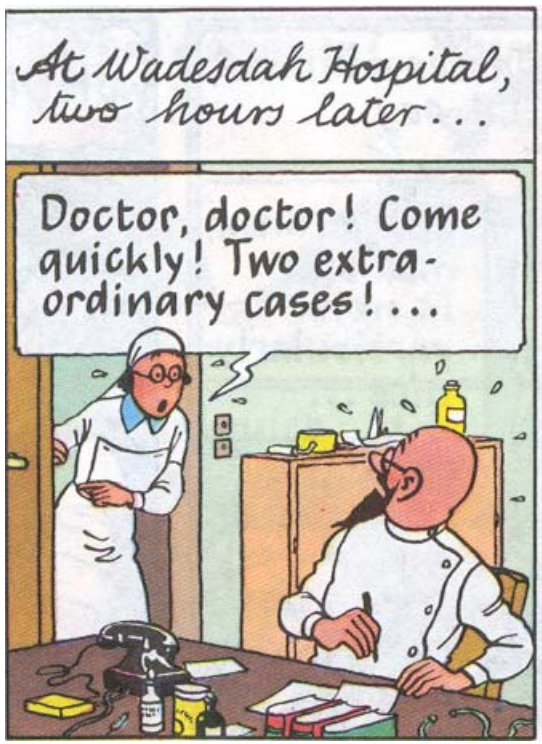
Some drugs while efficacious and used correctly...



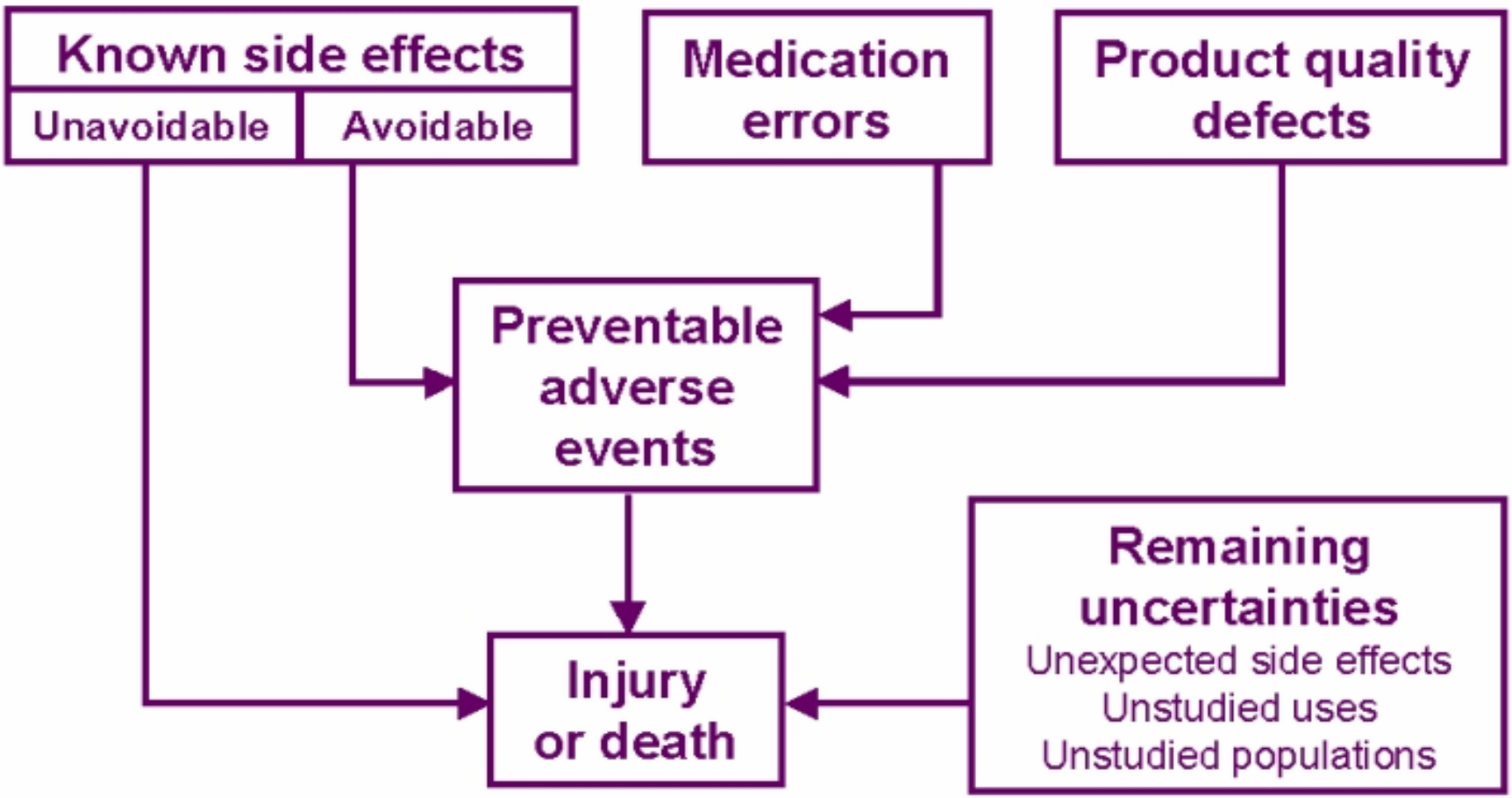
can cause side effects. Also...



drugs might not always be used as they were originally intended...

drugs might not always produce the desired effect…

Sources of Risk from Drug Products



Pharmacovigilance in pharmaceutical Industry

Main Business Objectives:

- Minimise Risks for Patients
- Minimise Risks for Company
- Meet Global Regulatory Requirements ➔ Full compliance
- Prolong Life-Cycle of Products
- Provide Competitive Advantage

Sources of Adverse Events (AE) reports

- Spontaneous reports (SRs):
  - Health Care Professionals (HCPs)
  - Non Health Care Professionals (non-HCPs)
- Literature cases
- The internet

Sources of Adverse Events (AE) reports

- Solicited reports:
  - Clinical trials phases I-IV
  - Observational Post-Marketing Surveillance (PMS) studies

- Stimulated reports:
  - Patient support programs
  - Disease management
  - Marketing surveys
  - Registries
  - Pharmacoeconomics
  - Class action lawsuits
  - Quality of life questionnaires

Sources of AE Reports
SRs from HCPs versus non-HCPs

- Spontanously reported from any source: physicians, pharmacists, consumers, lawyers etc.
- Every attempt to obtain medical verification of consumer reports
- Emphasize report quality over source type; triage appropriately
- Report consumer cases to HA if required even if they can not be medically confirmed (only mandatory in US and Canada)
- Include consumer reports in Periodic Safety Update Reports (PSURs)
- Include consumer reports in signal detection/analysis
- Protect patient privacy

Sources of AE Reports
Literature cases

- Companies should screen at least two major databases at least once a month
- Literature screening should cover cases in local journals
- Do not monitor broadcast and lay media, but do not ignore potential cases from these sources
- Treat unspecified generics as your own brand

Sources of AE Reports
The Internet

- New challenge
- “Identifiable patient” refers to a real person that can be validated
- Surfing non-company web sites is unnecessary, but should be done selectively to manage specific safety issues
- Screen all company web sites for AEs daily
- Maintain global consistency in approach

Sources of AE Reports
Solicited Reports

- Clinical Studies Phase I-IV
- Observational Post marketing Surveillance studies
- Investigator and sponsor causality required for reporting purpose

Sources of Individual Reports
Stimulated reports

- Important to distinguish from “solicited” reports
- Usually originate in the course of interaction with patients
- Handle as study reports - causality is needed even if difficult to assess
- Report under guidelines for post-marketing studies

Good Case Management
Follow-up Procedure

- Prioritize by the value of the case
- Highest priority for serious/unlabeled, followed by serious/labeled, then non-serious/unlabeled
- Non-serious/labeled should not be followed up if the 4 criteria are met
- Treat special issues and events that might lead to label changes as high priority

Good Case Management
Follow-up Procedure

- For priority cases, obtain as much information as possible during the initial contact
- The extent of follow-up detail solicited should be driven by the seriousness and expectedness (use CIOMS triage algorithm)
- For serious unlabeled cases, follow up until the long-term outcome is known
- If reporter does not cooperate with telephone follow-up, send written reminders
- Acknowledgment letters should be sent to suppliers of follow-up
- Do not encourage rechallenge

Limitations Of Clinical Trials

- Limited Size
- Short Duration
- Narrow Population
- Narrow Set of Indications
- Concomitant Medications

Observation of AE's in Clinical Trials

No. of Patients	Threshold for ADR	Probability
2,000	1 / 500 (Lymphoma fron Azathioprine)	0.98
	1 / 1,000 (Eye Damage from Practolol)	0.86
	1 / 5,000 (MI in Older Women from OCP)	0.33
	1 / 10,000 (Anaphylaxis from Penicillin)	0.18
	1 / 50,000 (Aplastic Anemia from Chloramphenicol)	0.04

Factors Effecting Spontaneous Reports

- Volume of use
- Duration on Market
- Severity of Reaction
- Labelled Status
- New Molecular Entities
- Manufacturer
- Publicity
- Calendar Year
- Awareness of Reporting

Limitations Of Spontaneous Reports

- Adverse Event Recognition
- Under Reporting
- Estimated Exposure Data
- Quality of Reports

Strengths of Spontaneous Reports

- Broad Exposure
- Cost Effective
- Signal Generation
- Represents Every Day Use

Regulatory Safety Reporting Requirements

- International standard in general:
  - Serious unexpected suspected adverse reaction
  - Unblind reportable Clinical Trial (CT) cases
  - Suspected fatal/life-treatening CT cases ➔ 7 calendars days
  - All other reportable serious suspected SRs and CTs ➔ 15 calendars days
  - Update of labeling reference document as appropriate
  - Notification to all investigators & ethis committees/IRBs

Regulatory Safety Reporting Requirements

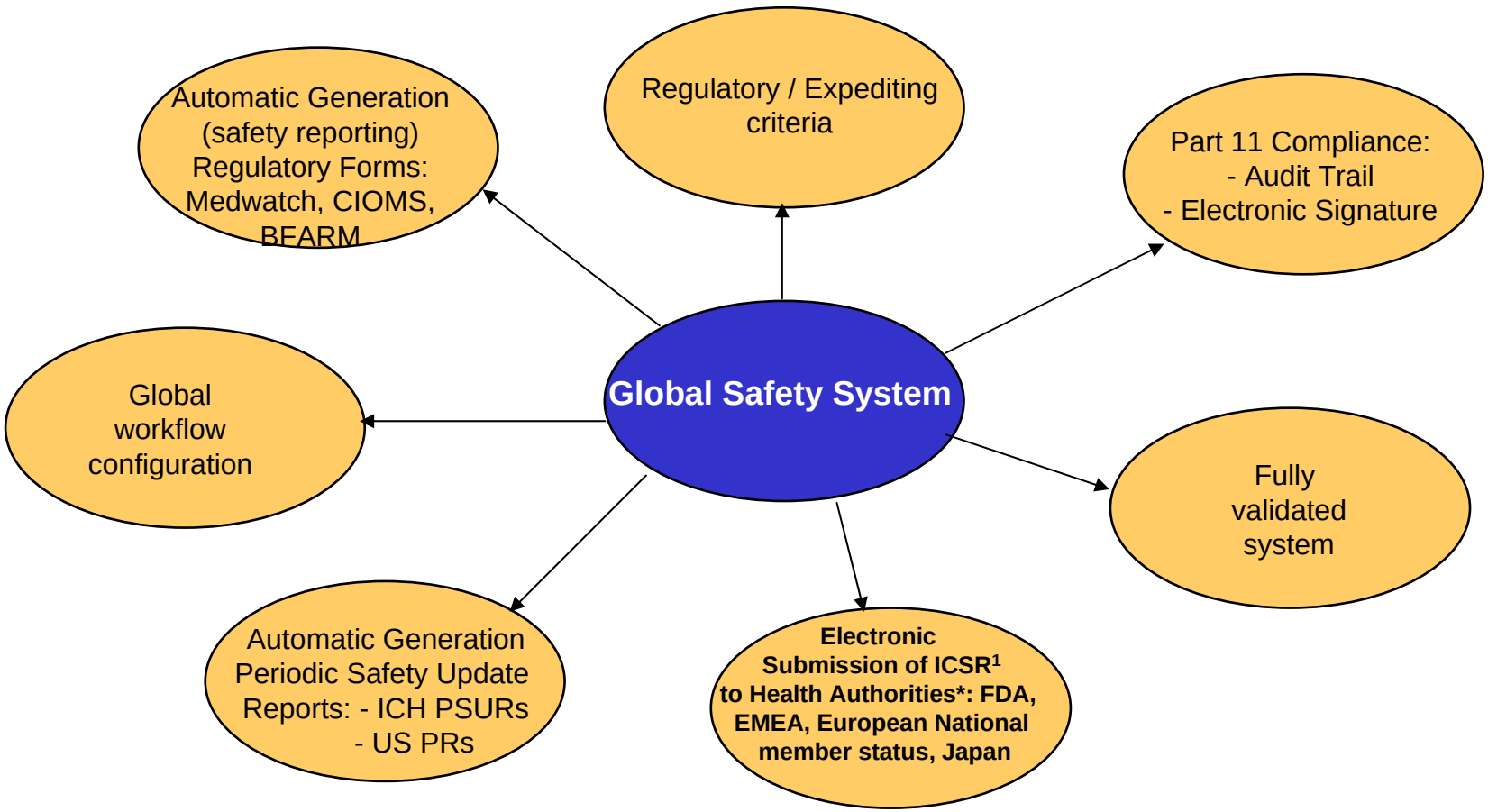
- National requirements beyond accepted international standards. Example of:
  - France: all **study**-related serious adverse reactions
  - Ireland: all serious adverse reactions irrespective of labeling, unblinded occuring in domestic centres
  - USA: all fatal & life-trreatening SAEs irrespetive of causality within 7 days for very specific drugs: genetically engineered
  - Finland, India, Norway, Slovakia, Switzerland: all domectic SAEs irrespective of causality

Standard Pharmacovigilance Activities

- Protocol review - to ensure proper collection SAEs/AEs
- Adverse event coding glossary review
- Clinical trial report - safety sections
- Investigator's Brochure - safety sections update
- Integrated Safety Summary (ISS)
- Preparation Periodic Safety Update reports
- IND and EU Annual Safety Reports
- Core Data Sheet – Safety Sections Update

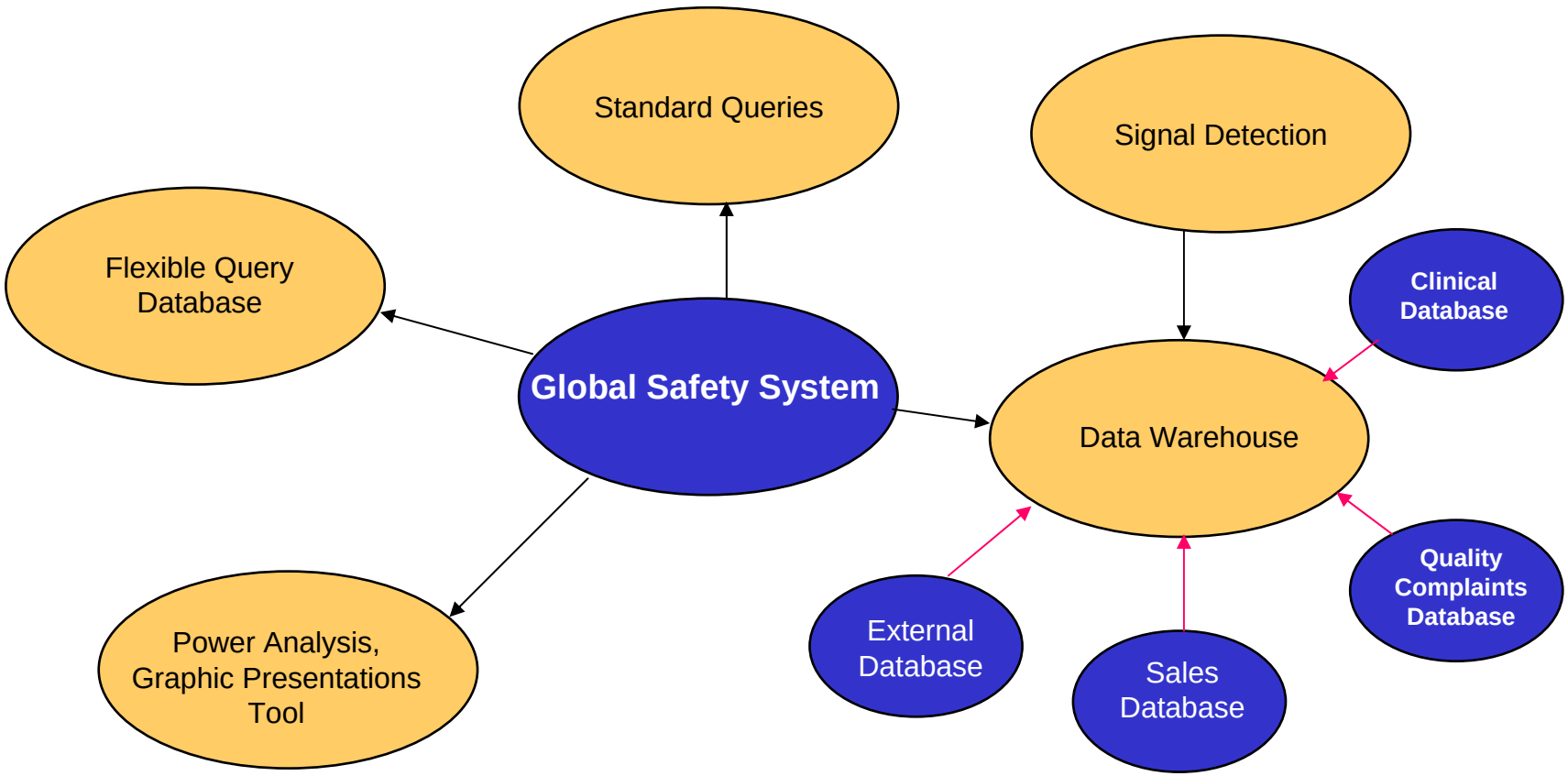
Global Safety Database

Compliance Component



Global Safety System

Pharmacovigilance Component



Safety Monitoring & Signal Identification

What is a signal?

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information."

T. Delamothe (1992) - WHO definition

Safety Monitoring & Signal Identification

- **Purpose**
  - Assess benefit/risk ratio
  - Identification of potential issues/signal identification
  - Provision of relevant information on potential side-effects to investigators and agencies
  - Propose/take action

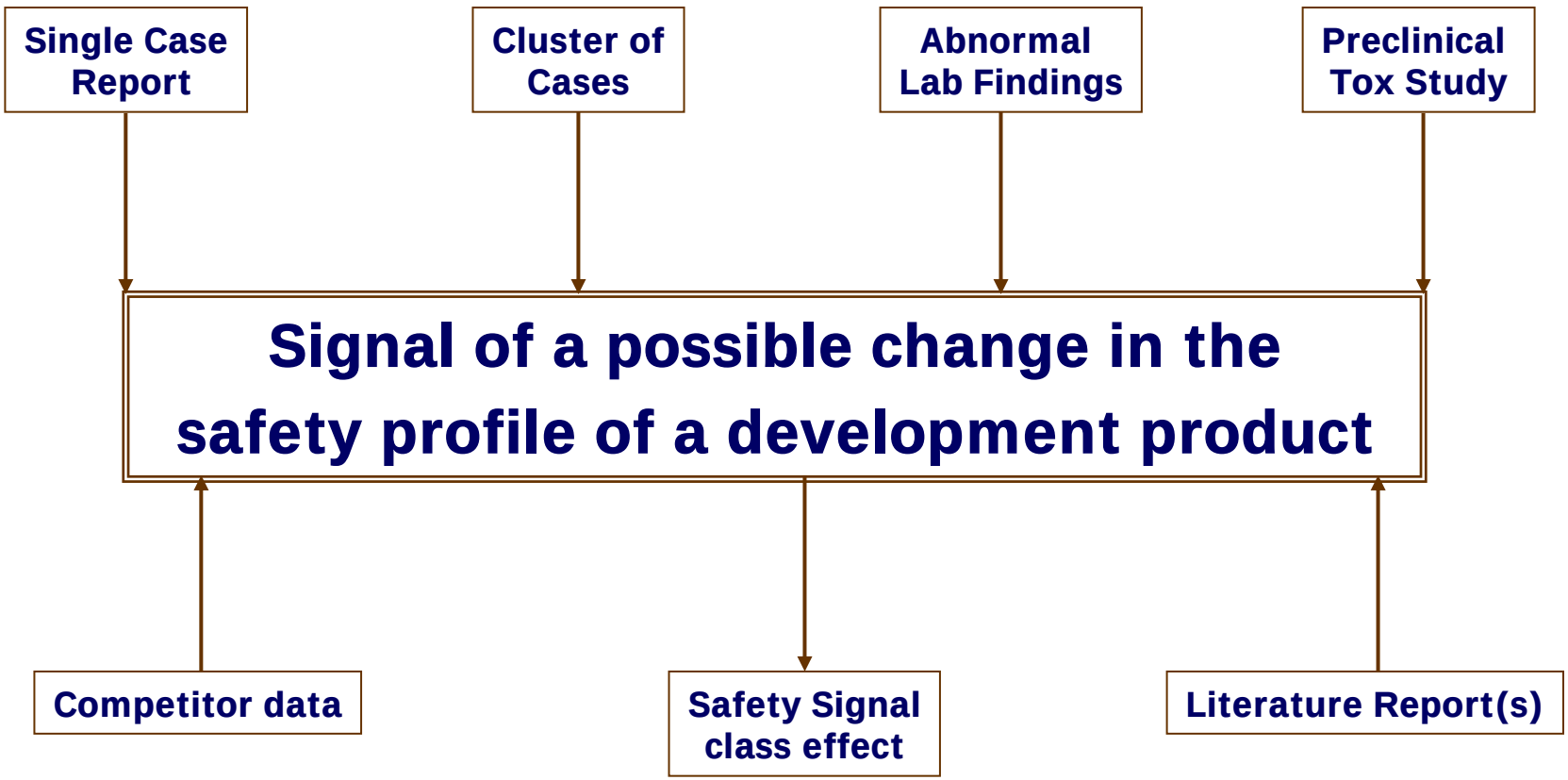
Safety Monitoring & Signal Identification

- **Prerequisites:**
  - Accuracy and completeness of data
  - Proper collection and follow-up of AE reports including proper source data verification
  - Standardised coding and assessments
  - Powerful analysis tool
  - Signal identification tool – Adequate Methodology/Treshold

Signal Generation Sources

- Report(s) of unexpected and serious AEs
- Expected AEs
  - increased frequency
  - greater severity
  - long-term sequelas
  - new risk factors
- Evidence from formal studies
- Change in efficacy
- Risks are greater than with alternative therapies with similar efficacy

Safety Monitoring & Signal Identification



Approaches to Signal Assessment

- Number of reported cases ➔ poor
- Pre-defined threshold values ➔ e.g. expected morbidity/mortality rate in treated population
- Statistical signal detection system
- Epidemiological investigation of signals
- Excruciating review by physicians, scientists and epidemiologists
- Reactive: Sit and wait! ➔ Do not trouble troubles until troubles trouble you!!
- Proactive ➔ Prompt action

Electronic Signal Generation and Evaluation

- Notification of “first ever” event with product
- Enter signal/ADE term II generate notification when defined threshold exceeded
- Trend analysis; notification of sudden increase in numbers of reports
- Proportional Reporting Ratio

Signal Detection Tool - Future

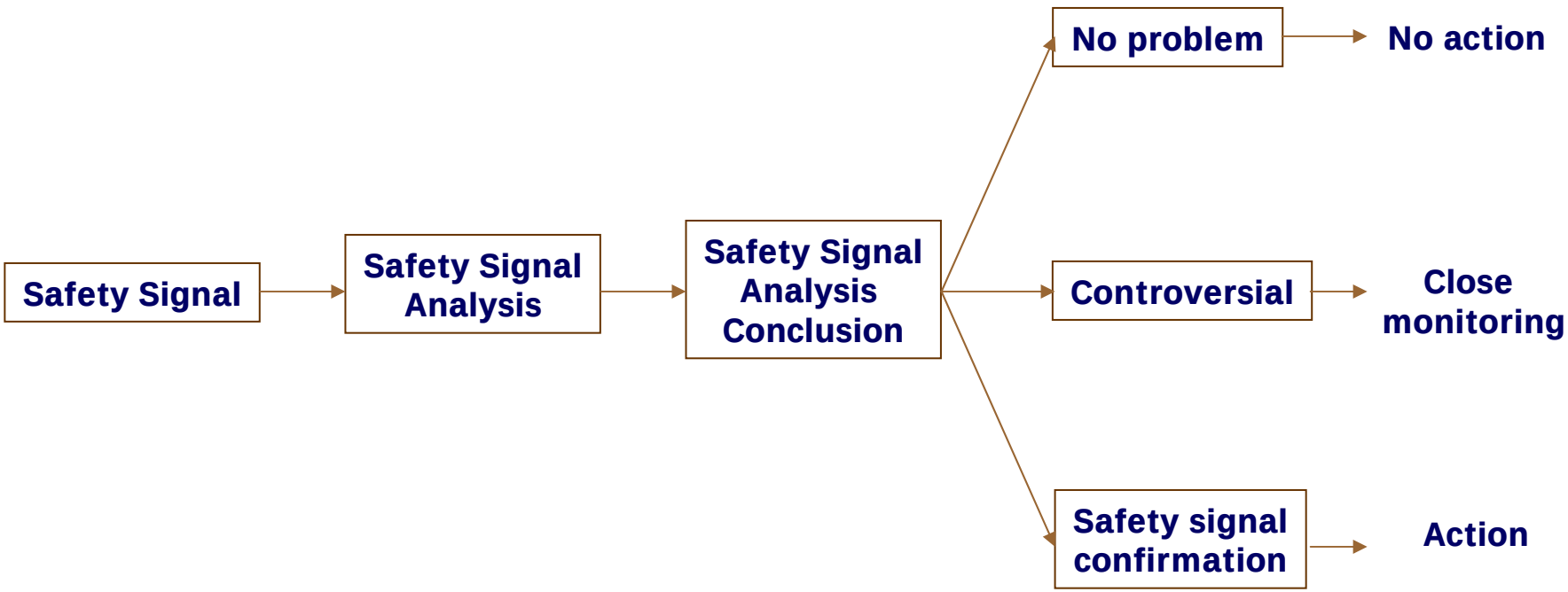
- Integrate with Development Data Warehouse
- Use AERs and WHO data for PRR method
- Compare against competitor drugs in same class
- Compare multiple arms in a trial for incidence rate differences
- Evaluate integration of IMS sales data

Safety Monitoring and Signal Identification

Limitations:

- Blinding
- Size of treated population → identify mainly frequent type A ADRs (wide exposure post-marketing)
- Selected population (exclusion criteria) versus misuse Post-Marketing
- High morbidity/mortality population → early judgement difficult
- Lack of background prevalence/incidence rates
- Poor quality of spontaneous reports – Unconfirmed diagnosis
- Safety culture within the company → very defensive approach rather than fact oriented

Safety Monitoring and Safety Identification



Safety Signal Confirmation

Action to be taken varies according to the seriousness of the issue and the benefit/risk assessment:

- Amend labelling – boxed warning
- Amend protocol, e.g. dose, exclusion criteria, infusion rate etc.
- Keep on hold a specific trial
- Keep on hold the whole project
- Terminate the project
- Product recall
- Safety alert
- Post-marketing or epidemiological studies

Working Towards Proactive Pharmacovigilance

Phase I

Phase II

Safety Surveillance/Monitoring

Phase III

Phase IV

ICH E2E Proactive Pharmacovigilance Plan

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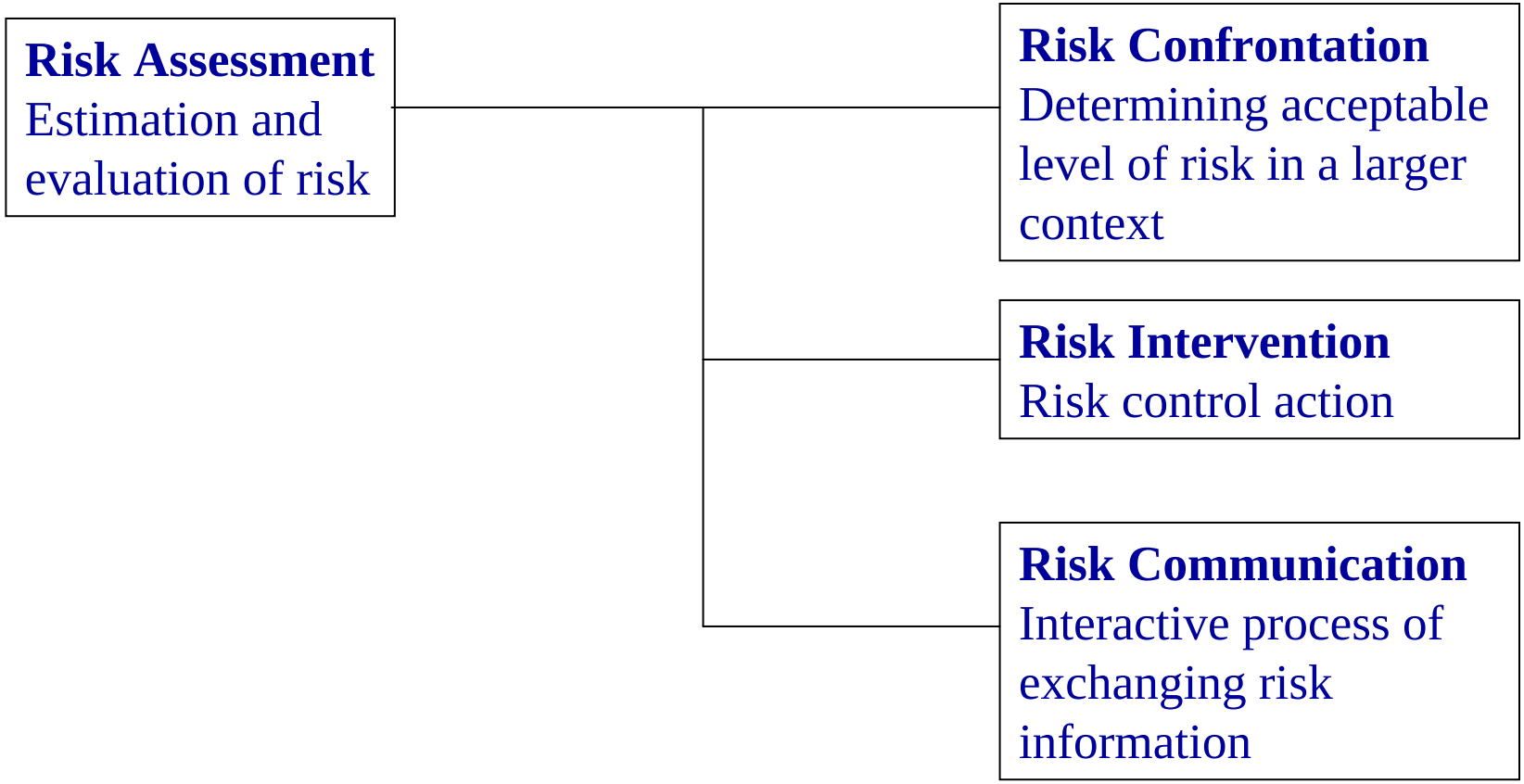
Risk Management Program

ICH E2E: Prospective Planning of Pharmacovigilance (PPP)

- Pharmacovigilance specification:
  - Discussed with regulators **pre-approval ➔ focus on early post-marketing period**
  - Established risk of a drug
  - potential for significant unidentified risk
  - potential at risk populations and situations that have not been studied pre-approval
- Pharmacovigilance plan:
  - driven by the pharmacovigilance specifications
  - **will be shared and scrutinized by the regulators assessing the licensing application in the different ICH regions**
- Post-approval safety studies:
  - for products with risks or concerns
  - at-risk groups which have not been studied

Risk Management Plan



Pharmacovigilance – Life Cycle Approach

- **Patient Population Epidemiology**
  - Incidence - Prevalence,
  - Natural history - Comorbidity
  - Drug utilization patterns
  - Risk - preventive factors
  - Etiological factors
- **Safety Issues Review**

- **Safety Monitoring**
  - Preclinical Safety data
  - Clinical pharmacology
  - AEs from clinical trials
  - HA “hot topics”
  - Expected patient safety
  - Risk management plan
- **Safety Signal Evaluation**
- **CT Design - Simulations**
- **Disease awareness**

- **Safety Signal Generation**
  - Internal and external
- **Safety Monitoring Post-Marketing Reports**
  - Drug utilization
  - Long term safety
  - Risk Management
  - Additional benefits

Pharmacovigilance into the future

working towards

- **INTEGRATED**
- **PROACTIVE**

Development and life-cycle management of the drug