Risk Management Strategies
Why DILI initiative is important

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President of the Council of International Organisations for Medical Sciences (CIOMS)
Immediate Past President of the International Society of Pharmacovigilance
Ex-PRAC Member

Burden of Adverse Drug Reactions (ADRs) in EU

- 5% of all hospital admissions,
- 5% of all hospital patients,
- 5th cause of hospital death,
- 197 000 deaths per year caused by ADRs,
- Average cost of an ADR : 2 250 €,
- EU Societal cost of ADRs Euro 79 Billion / year.

High percentage of ADRs are preventable

Even a small improvement in PV system will have a major impact on public health and society.

Objectives of Pharmacovigilance

- Protect and promote public health

- Post-marketing surveillance of products
  - Reduces uncertainty regarding known hazards
  - Generates new information regarding unknown risks

- Health effects of Pharmacovigilance are achieved through regulatory actions informed by newly generated information in the post-marketing setting

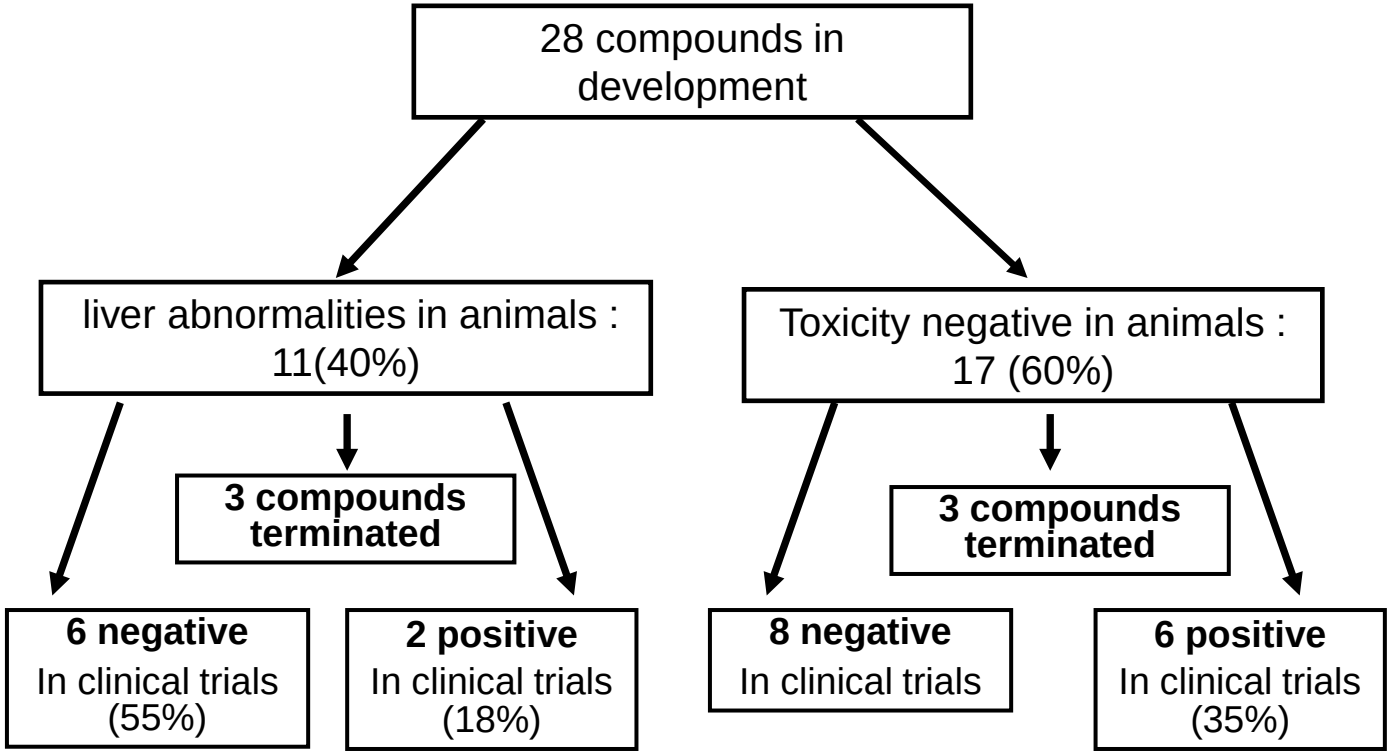
Why do we need Pharmacovigilance?

Preclinical studies are difficult to extrapolate to humans because

- Small number of animals and limited duration of the observation,
- Pharmacokinetic differences between animals and humans,
- Some events can not be observed with animals,
- Difficulty to reproduce human disease on animals.

Prediction of hepatotoxicity from animal data

Ballet F. Hepatotoxicity in drug development: detection, significance and solutions. J.Hepatol 1997



Why do we need Pharmacovigilance?

In clinical trials

- Main purpose: Therapeutic efficacy of the drug in the targeted indication,
- Administration to a standardized population (not representative of the overall population),
- Small size of the study population (Difficult to observe rare effects),
- Very few or no data on long term usage (cancer, dementia…),

Right drug at the right dose at the right regimen to the right

Number of subjects per Clinical Trials (CT)

Medicines:	Number of subjects per CT:
Chemical drugs	1000-5000
Biologic products	100-1000
Biosimilars	100-500

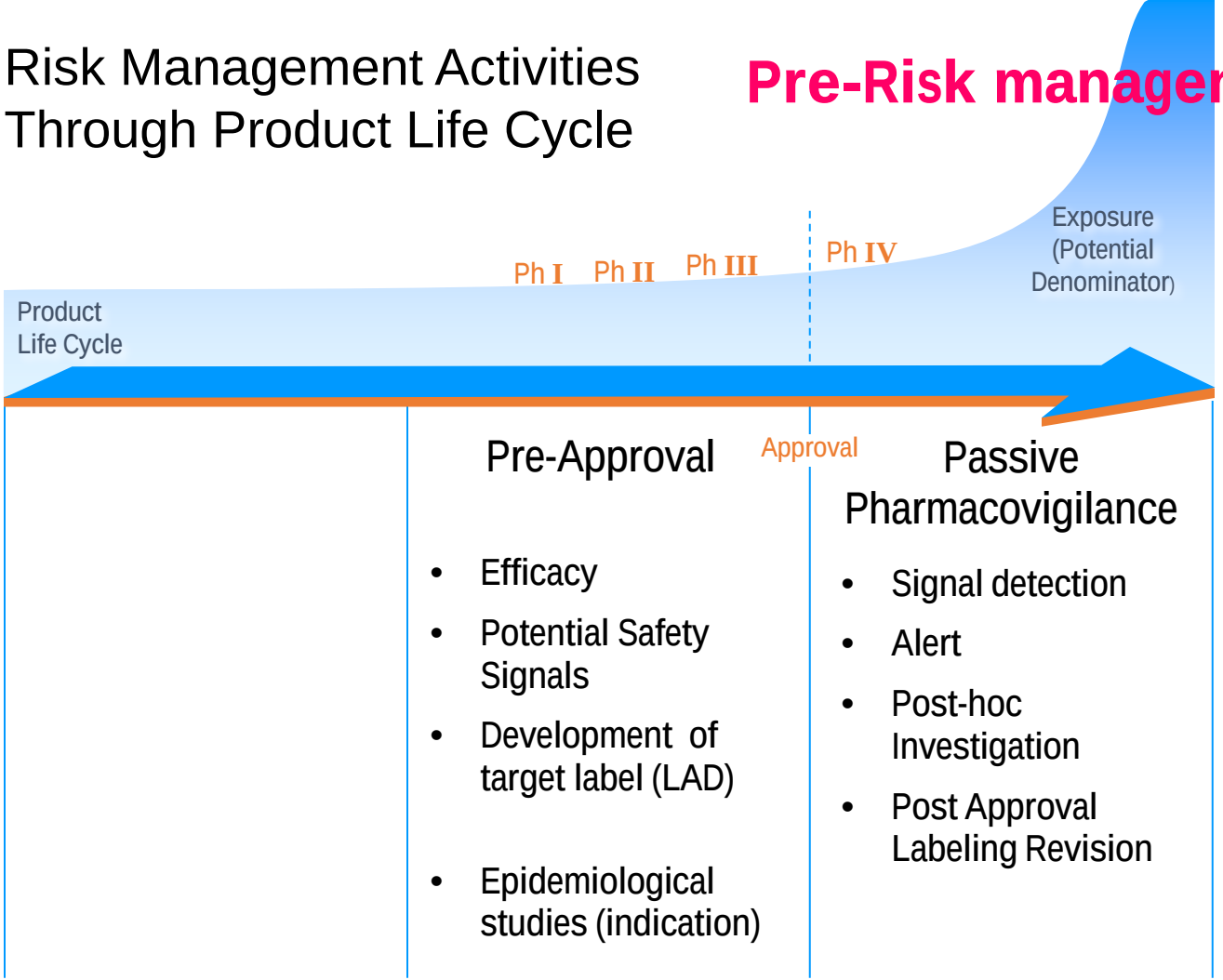
Drug information journal

Why do we need Pharmacovigilance?

In the post-marketing

- The product will be used in different conditions, at different doses and with different regimen,
- Large number of individuals,
- New safety data on long term usage,
- Be used in patients with multiple concurrent conditions and on multiple concurrent medications.

Risk Management Activities Through Product Life Cycle



Consequences

- To rely only on spontaneous reporting may lead to extreme regulatory decisions and reduces benefits to target population with Product withdrawal, delay or refusal of marketing

- These extreme actions should only be used when the benefit/risk ratio is either unacceptable or non-manageable

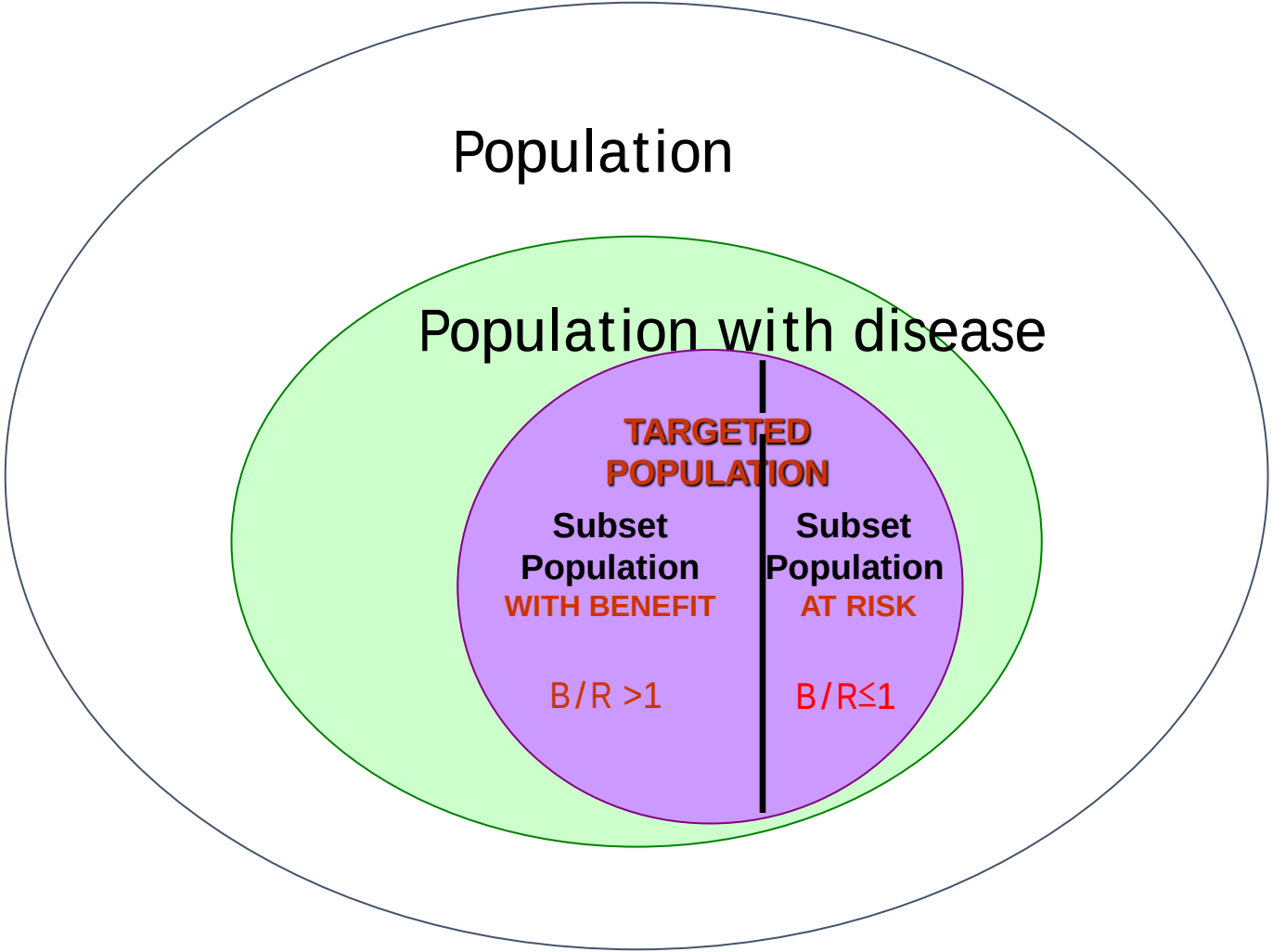
Scope of Pharmacovigilance

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO)

Pharmacovigilance in this presentation goes beyond this

Management of the benefits and risks of medicines

on the market


Population
Population with disease
TARGETED POPULATION
Subset Population
WITH BENEFIT
B/R >1
Subset Population
AT RISK
B/R≤1

Risk management perspective

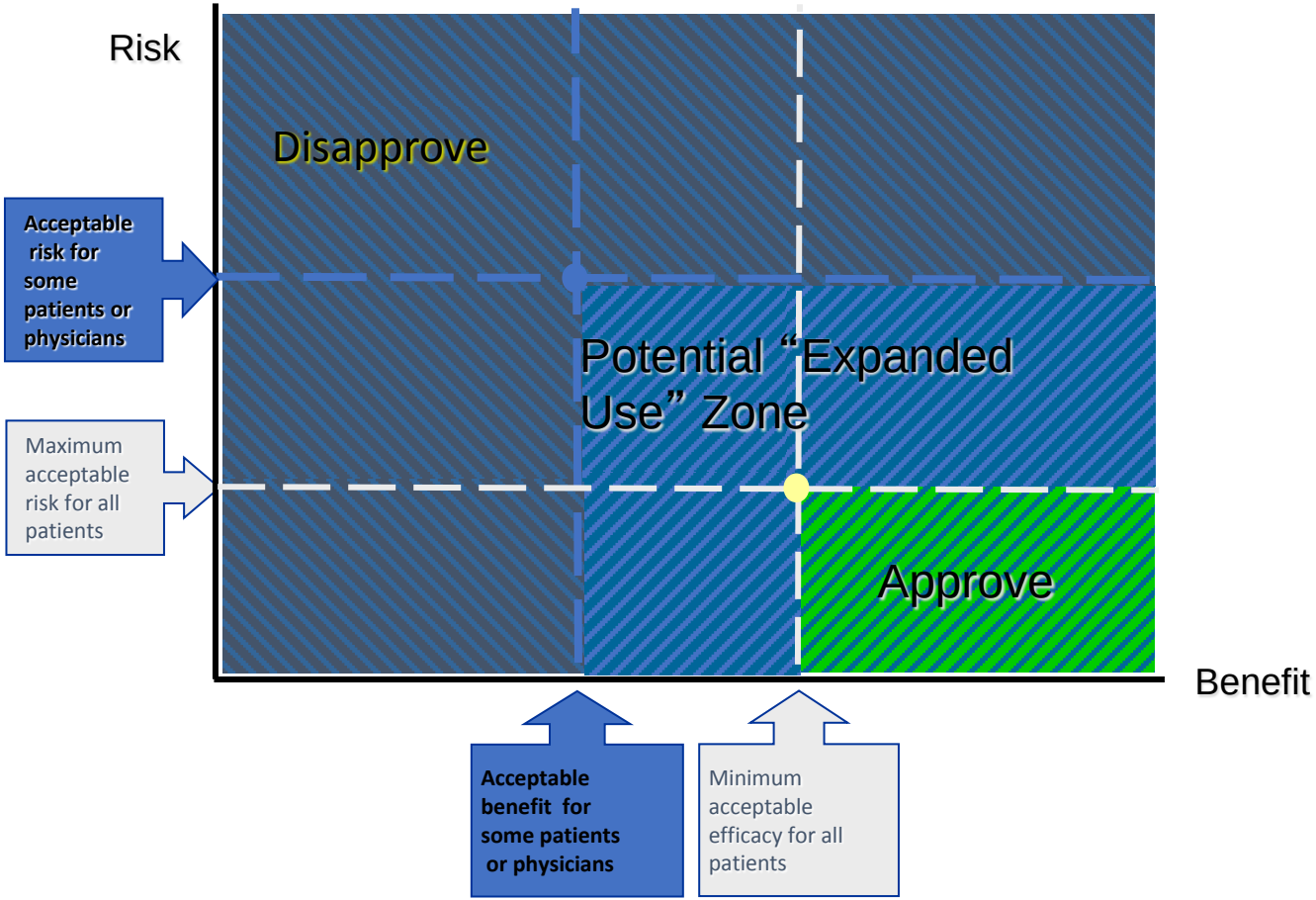
Efficacy for all patients

with acceptable risk for all patients

Risk management

Efficacy for a subset population of patients

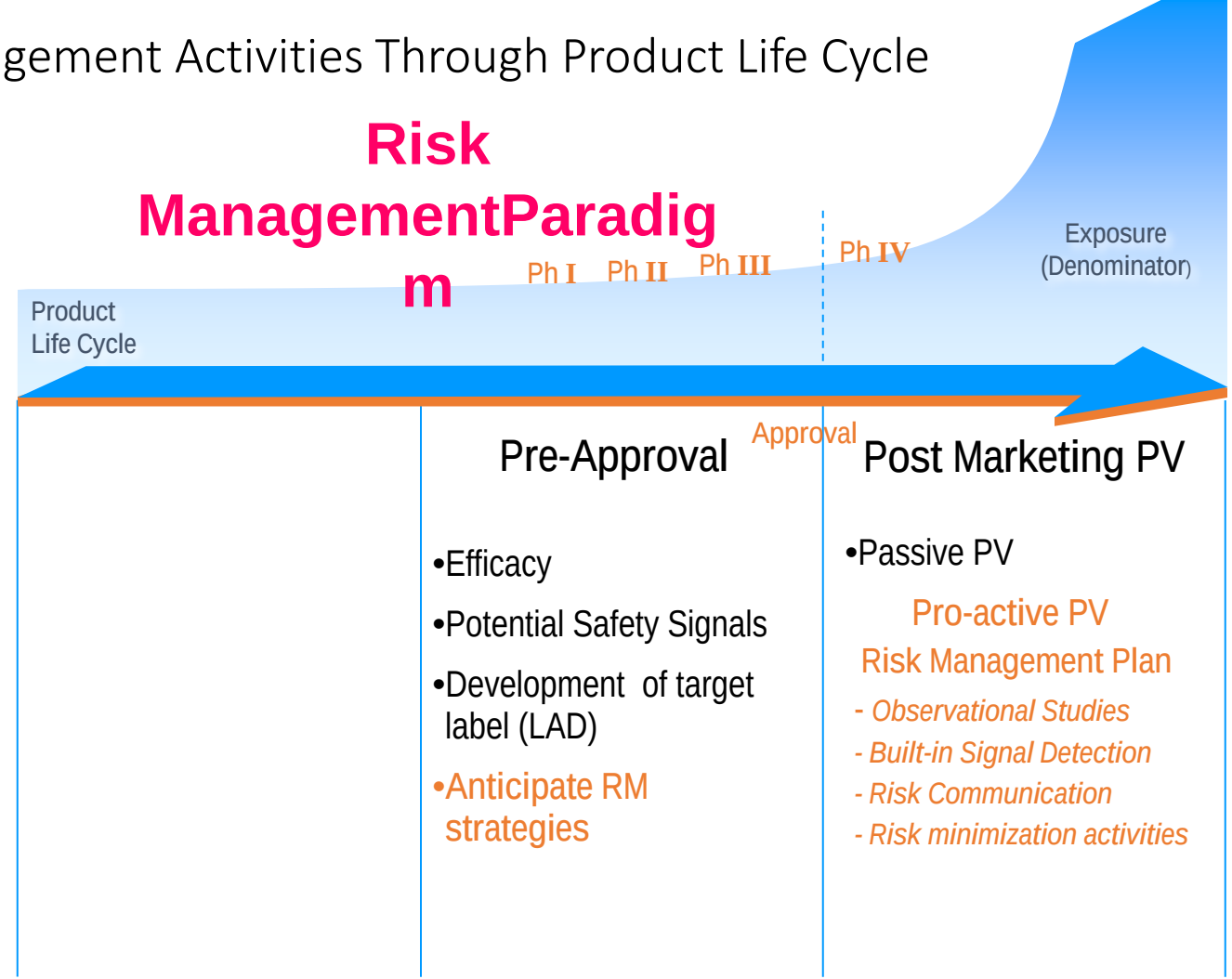
with acceptable risk for this subset population


Risk
Disapprove
Acceptable risk for some patients or physicians
Potential "Expanded Use" Zone
Maximum acceptable risk for all patients
Approve
Benefit
Acceptable benefit for some patients or physicians
Minimum acceptable efficacy for all patients

Strategy

- Proactivity
- Risk AND benefit assessment in real life
- Proportionality : an action should not be more severe than necessary
- Impact measure

Risk Management Activities Through Product Life Cycle



The EU Risk Management Plan

Part I Product(s) Overview

Part II Safety Specification

- **Module SI: Epidemiology of the indication(s) and target population(s)**
- **Module SII: Non-clinical part of the Safety Specification**
- **Module SIII: Clinical trial exposure**
- **Module SIV: Populations not studied in clinical trials**
- **Module SV: Post-Authorisation Experience**
- **Module SVI: Additional EU requirements for the Safety Specification**
- **Module SVII: Identified and potential risks**
- **Module SVIII: Summary of the safety concerns**

Part III Pharmacovigilance Plan

Part IV Plans for post-authorisation efficacy studies

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)

Part VI Summary of the RMP

Part VII Annexes

Part I Product(s) Overview

Part II Safety Specification

Important Identified Risk
Important potential Risk
Important Missing Information

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Part III Pharmacovigilance Plan

Routine PV and other solutions

Part IV Plans for post-authorisation efficacy studies

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Solutions for post-marketing safety monitoring

- **Spontaneous reporting:**

  Main safety net to detect new AEs population-wide,

- **Active pharmacovigilance:**

  For important potential risks,

- **Observational studies, registries, large simple trials:**

  Databases or *ad hoc (evaluation of potential risks).*

Observational studies, Large Simple Trials and Registries (1)

- For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, (but can be limited by low statistical power).

Observational studies, Large Simple Trials and Registries (2)

It is difficult to use clinical trials:

- to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications,
- to identify risk factors for a particular adverse event.
- when the event rates of concern are less common than 1:2000-3000.

But, for evaluation of more common events, which are often seen in untreated patients, clinical trials are preferable to observational studies.

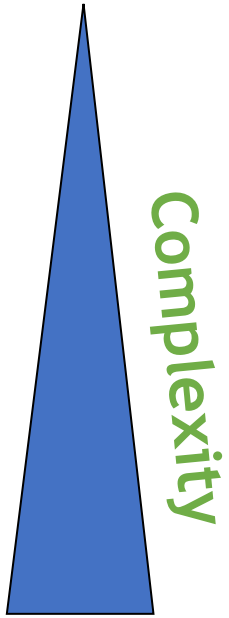
Observational studies, Large Simple Trials and Registries (3)

Role of Registries

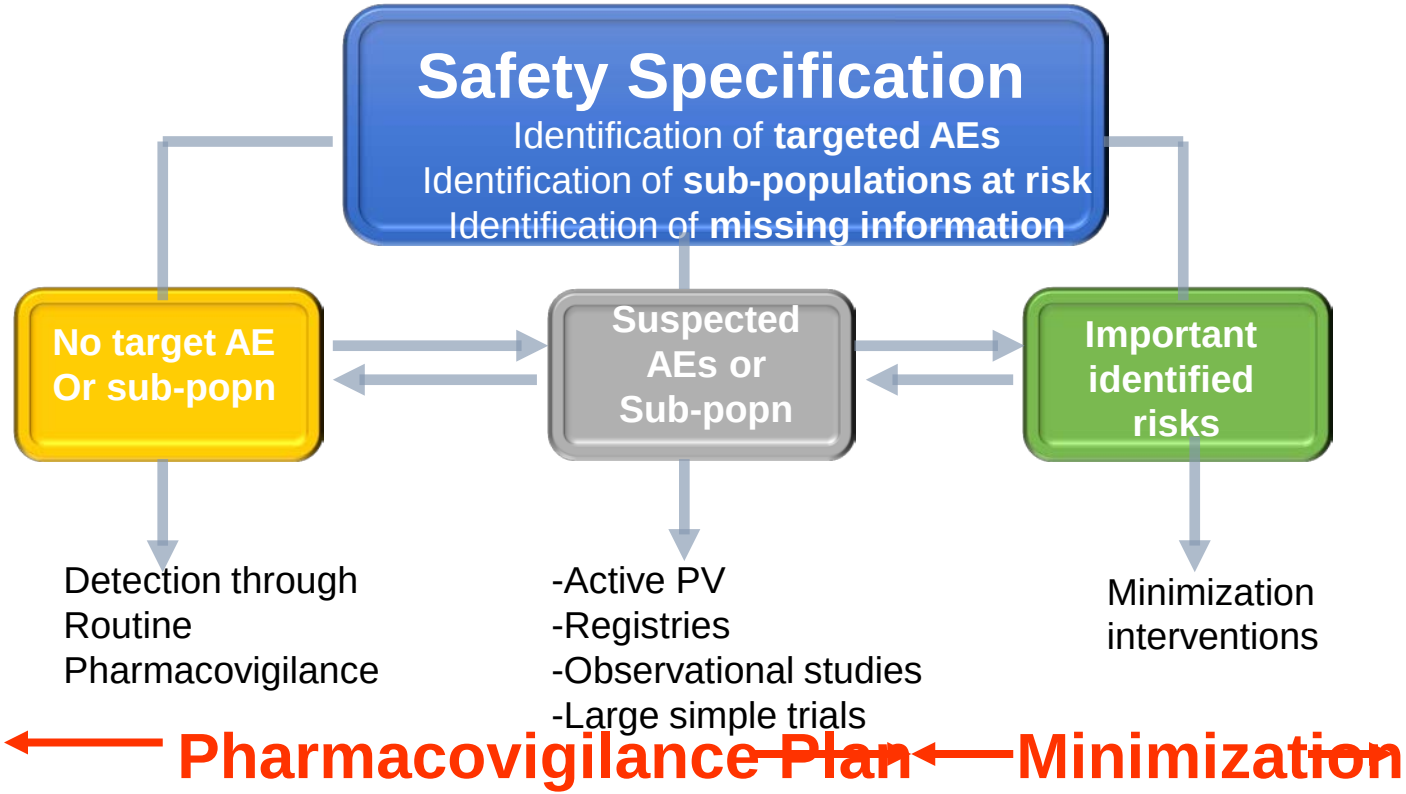
- Small Market, orphan drugs, low prevalence condition, Biologics, etc.
- North America : often associated with controlled prescription program;
- Europe : can be implemented everywhere, especially in country without databases.

Main Intervention Tools

- Education material to physicians and/or patients
- Medication guide endorsed by health authorities
- Informed consent
- Academic detailing
- Physician authorization (sticker)
- Restricted distribution
- Registries (voluntary or mandatory)



Pharmacoepidemiology Strategy and Tool Box



The CIOMS DILI Working Group

Acronym & Logo

Council for
International
Organizations of
Medical
Sciences

- ***Mission Statement***

  CIOMS mission is to advance public health through guidance on health research including ethics, medical product development and safety

CIOMS in short

- Organization located in Geneva :
  A. International
  B. Nongovernmental
  C. Not-for-Profit

- In official relations with WHO + Associate Partner of UNESCO

- ... for WHO, health authorities, academic organizations, pharmaceutical industry and other concerned stakeholders
  ➢ an organization of medical science organizations

- *Forum for discussion and neutral platform to elaborate new ideas in medical product development, pharmacovigilance and research ethics (bioethics)*

Organization

CIOMS

Executive committee

President: Prof. Hervé Le Louet - since Nov. 29, 2016 (member of PRAC)

Vice president: Prof. Samia Hurst (Swiss academy of sciences)

Secretary-General: Dr Lembit Rägo (CIOMS secretariat, former WHO Regulatory Unit Head)

<= 12 representatives (mostly from national and international members)

Secretariat

Secretary-General Dr. Lembit Rägo (since April 18, 2016) and team; located in Geneva (close to WHO und UN Palais des Nations)

Mandate: „day to day management in conformity with statutes and directions of executive committee“

CIOMS

Members Organizations - General Assembly

International Organizations (12)

National Organizations, Associate Members (11)

Associate Members (19)

Collaborations

Partners: Authoritative, international organizations dealing with related topics

e.g. WHO, PAHO/AMRO, ICH, IFPMA

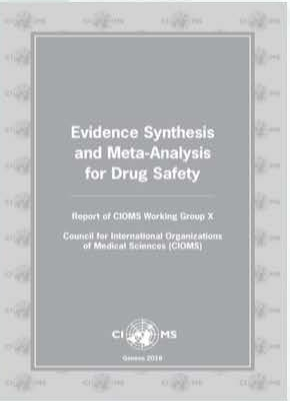
Historic landmarks

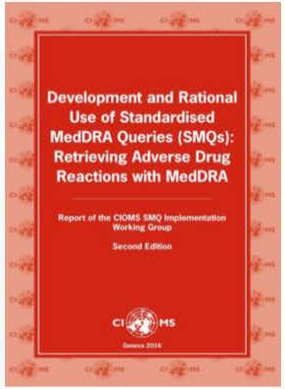
OUR HISTORY

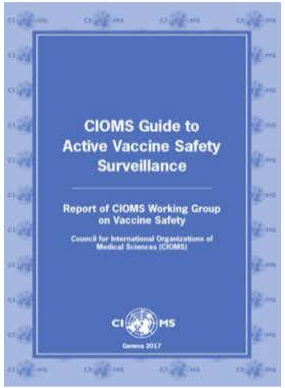
2016	New CIOMS Ethical Guidelines for Health-related research involving humans.
1993	Start of CIOMS focus on pharmacovigilance and reporting adverse drug reactions.
1982	Adoption by UN of CIOMS Medical Ethics for prisoners.
1977	Launch of Ethics of Research involving humans.
1959	Vienna meeting on controlled clinical trials.
1952	Present name CIOMS adopted.
1949	Council formally constituted in Brussels by WHO and UNESCO.

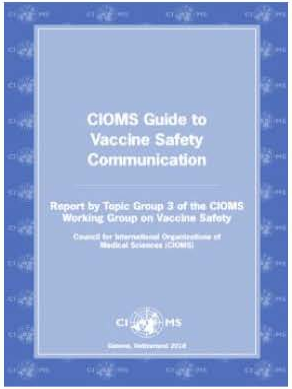
Pharmacovigilance: Recent Safety Publications

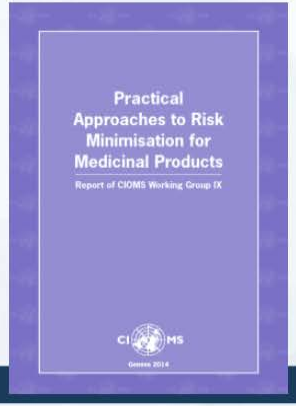
https://cioms.ch/shop/product-category/recently-published/

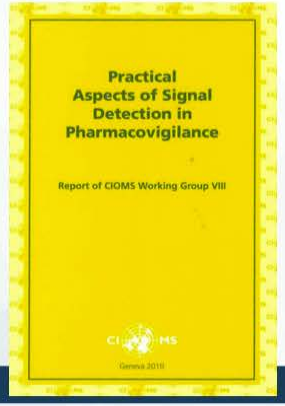


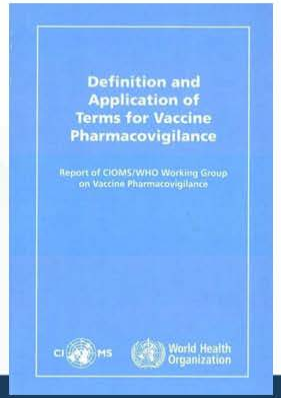












CIOMS Working Groups are Core:
Composition (1)

- CIOMS Working Groups are international – they try to involve experts from different countries and regions
- CIOMS Working Groups are usually composed of all important stakeholders, in many cases of
  - Regulators
  - Academia
  - Industries
  - WHO (as member/observer of the group)
  - …
- They involve also representatives of interested in the topic member organizations
- In some working groups representatives from organizations such as ICH could also participate e.g. ICH secretariat in CIOMS WG on MedDRA Standardized Queries (SMQs)

Why a CIOMS/WG on DILI

- DILI is a growing challenge because of the ever increasing number of drugs used in medical care. It is responsible for more than 10% of all cases of acute liver failure posing a major clinical and regulatory challenge.
- Hundred drugs and herbal medicines have been associated with DILI. In many instances, the hepatotoxic potential of a drug can only be recognized post-marketing and DILI is one of the most frequent reasons for marketed drug withdrawal and modification of labelling.
- The clinical pattern of DILI is diverse and can mimic almost any form of liver disease. making it difficult for an easy and early diagnosis.
- DILI remains largely unpredictable and is not amenable to efficient preventive measures. It therefore remains a public health issue as it is an important cause of mortality and liver transplantation, and a leading cause of attrition in drug development.
- Several initiatives (Universities/regulators/industries) that need to be coordinated to avoid redundancies, improve dissemination and widen the audience

Issues (1)

About the diagnosis

- The diagnosis of DILI is a challenge since there is currently no test from imaging, histology, biology or other biomarker evaluation that is sensitive and specific enough to ascertain that a patient develops hepatotoxic reaction to a xenobiotic, at any stage of severity;
- The diagnosis still relies on a comprehensive clinical assessment and published case reports and spontaneous reports. Liver biopsy allowing direct examination of the tissue remains the gold standard for the study of the pathophysiological steps but is not routinely used.
- The diagnosis of DILI continues to be based on finding abnormalities of standard biochemical liver tests, (ALT,AST,ALP, GGT) and conjugated bilirubin. Although liver enzymes lack of specificity, liver injury in the context of DILI has been defined as an elevation of ALT, conjugated bilirubin or ALP.

Issues (2)

About the causality assessment

- Adverse drug reaction (ADR) causality assessment is a routine procedure in pharmacovigilance
- Despite some attempts for creating liver-specific causality assessment scales, such as the CIOMS/RUCAM (international consensus), Maria and Vitorino (Portugal) and DDW-J (Japan) scales, no method has been considered as the reference for DILI.
- The use of expert opinion to identify DILI is common practice for diagnosing hepatotoxicity. However this approach is subjective and lacks defined criteria

Need for a new ADR causality assessment algorithm dedicated to the liver.

Issues (3)

About predictive models

- Despite comprehensive preclinical drug testing and clinical trials, over 10% of drugs approved during 1975–2000 were either withdrawn from the worldwide market or restricted in use for safety reasons. From 2002 to 2011, in the European Union, seven drugs have been withdrawn from the market for that reason. This is mainly explained by failures in pre-clinical and clinical testing.

- Prevention of DILI is currently mainly focused on the development of new preclinical testing, and on research for more reliable biomarkers allowing early detection and monitoring for DILI during therapy.

Issues (4)

About Prevention

- Withdrawal of the offending medication is the most relevant intervention in the individual management of hepatotoxicity once detected; however, considering the lack of specific markers that distinguish transient self-resolving ALT increases from potentially serious DILI, the thresholds set for discontinuation of the offending drug remain pragmatic and recommendations varies.

- Recent progress in research on DILI has been determined by key developments in three areas
  - The *new technologies* allow the identification of genetic risk factors with improved sensitivity, specificity, and efficiency.
  - The new *mechanistic concepts* of DILI emphasize the importance of unspecific “downstream” events following drug-specific initial “upstream” hepatocyte injury and of complex interactions between environmental and genetic risk factors.
  - the *development of new biomarkers*: there are active initiatives underway to discover and qualify new biomarkers for DILI prediction, diagnosis and outcome. To accomplish these goals successfully, the role of the pharmaceutical industry is key and prospective DILI registries must adopt standard procedures for biological samples collection and storing.

Aim of the working group

To establish a balanced, efficient, global perspective on DILI detection, susceptibility factors, severity, outcome and probability through causality assessment tools, monitoring and management during the drug development and post-marketing phases.

Gaps to fill in

- Interpretation and management of liver safety signals, considering that DILI assessments differ between clinical practice and clinical trials.
- Guidance on data analysis from patients with DILI included in clinical trials to reach a consensus on terminology and level of evidences needed to assess clinical liver safety, data standards, and data acquisition.
- Data capture and analysis of signals during premarketing clinical trials: to adopt standards for data and biospecimen acquisition and management, to allow future biomarkers development and validation.
- Defining the best causality assessment process in clinical trials to reflect the degrees of uncertainty in causal link.
- Guidance to assess liver safety from data for special populations with abnormal baseline liver tests in relation with cancer virus, NASH and paediatric patients.
- Validating traditional and new biomarkers: combining large liver safety datasets across many clinical trials in different patient populations to generate sufficient number of hepatic events.

Deliverables (1)

- Scenario and burden of DILI worldwide,
- Chemical hazards and susceptible hosts and its interactions,
- Identification of DILI Signals in clinical trials and during postmarketing monitoring,
- Clinical DILI assessment,
    - -Harmonization of nomenclature, clinical measurements, definitions,
    - -classification, patterns and outcomes,
    - -Diagnostic approach to DILI,

-In-depth analysis of existing re-challenge data to provide recommendations

-Standardization of the case report form for prospective multicentre data collection

-Standard operating procedures (SOPs) for the collection and storage of all biological samples related to phenotypic data in clinical trials, clinical research and prospective DILI registries.

Deliverables (2)

- Analysis, interpretation and quantification of DILI signals.
    - Hy's law and eDISH criteria according to the therapeutic area of the clinical trial
    - Assessment of the drug DILI potential and the benefit/risk balance
    - Assessment of the social acceptability of the risk

- Causality assessment methods for DILI
    - According to type of liver injury. Considering atypical DILI patterns: fibrosis, vascular, etc.
    - Taking into account all available information of the suspected culprit drug
    - Minimum criteria required for DILI assessment

- DILI in special populations: oncology, chronic viral infections, chronic liver disorders such as NASH and paediatrics.

- DILI Risk Management:
    - DILI Monitoring, for regulators, drug developers and drug users
    - Information to include in SmPCs regarding DILI
    - DILI Risk communication

- Risk minimization strategies, also considering support through personalized medicine approaches.

CONCLUSION

Strong need of a Working Group to address the present knowledge and practice gaps related to DILI in order to formulate pragmatic consensus-based recommendations to address the outstanding issues listed above.

Results in June

Muchas Gracias , Thank you ….

70 YEARS

CIOMS

1949 - 2019