Advances in the Science & Methods of Pharmacovigilance: Session 1

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SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON

DEPARTMENT OF GLOBAL HEALTH
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Institute of Health Education and Research

Series Learning Objectives

1. Describe issues and the challenges in the conduct of pharmacovigilance.
2. Explain a framework for assessing and improving drug and vaccine safety.
3. Demonstrate how pharmacovigilance methods and risk management strategies can be used in resource-limited settings.

Today's Session

- Overview and fundamentals
- Regulatory pharmacovigilance
- Framework for pharmacovigilance

Plan for Sessions #2 and #3

- Methods for risk identification, risk evaluation, risk management and communication
- Conducting PV in public health programs, including vaccine PV
- PV considerations for drug developers/industry
- Metrics and assessing the performance of PV systems

Contemporary Issues in PV

- PV and public health programs
- Metrics
- Harmonization
- Active surveillance
- Records linkage
- Epidemiologic methods for risk evaluation
- Social media

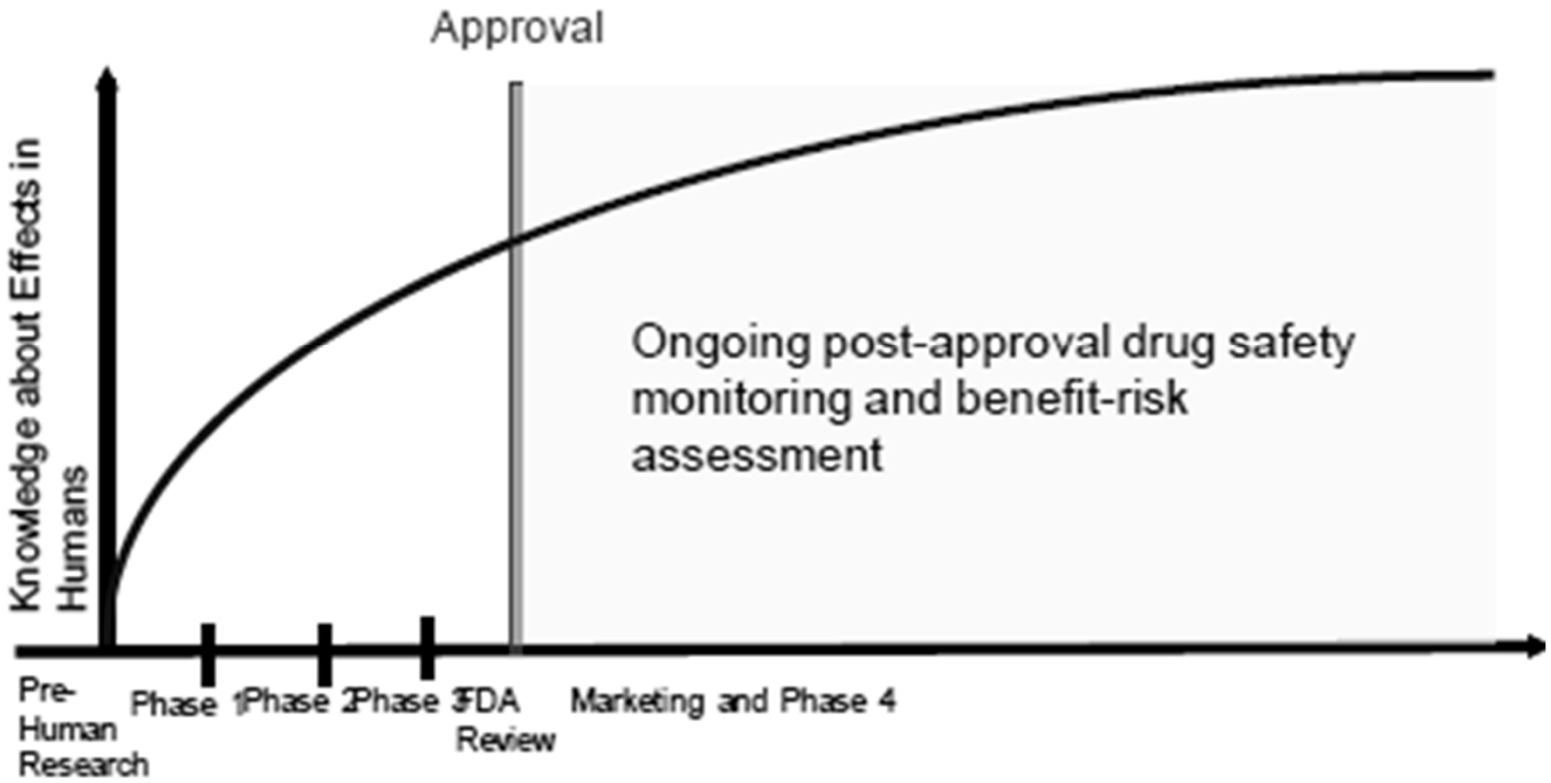
Disclosures

- My university receives research support for my work from the Bill & Melinda Gates Foundation, Wellcome Trust and the Fleming Fund.
- I serve as a member of the USP Expert Panel on Review of Surveillance and Screening Technologies for the Quality Assurance of Medicines.
- I am Editor-in-Chief of the *Journal of the American Pharmacists Association*.

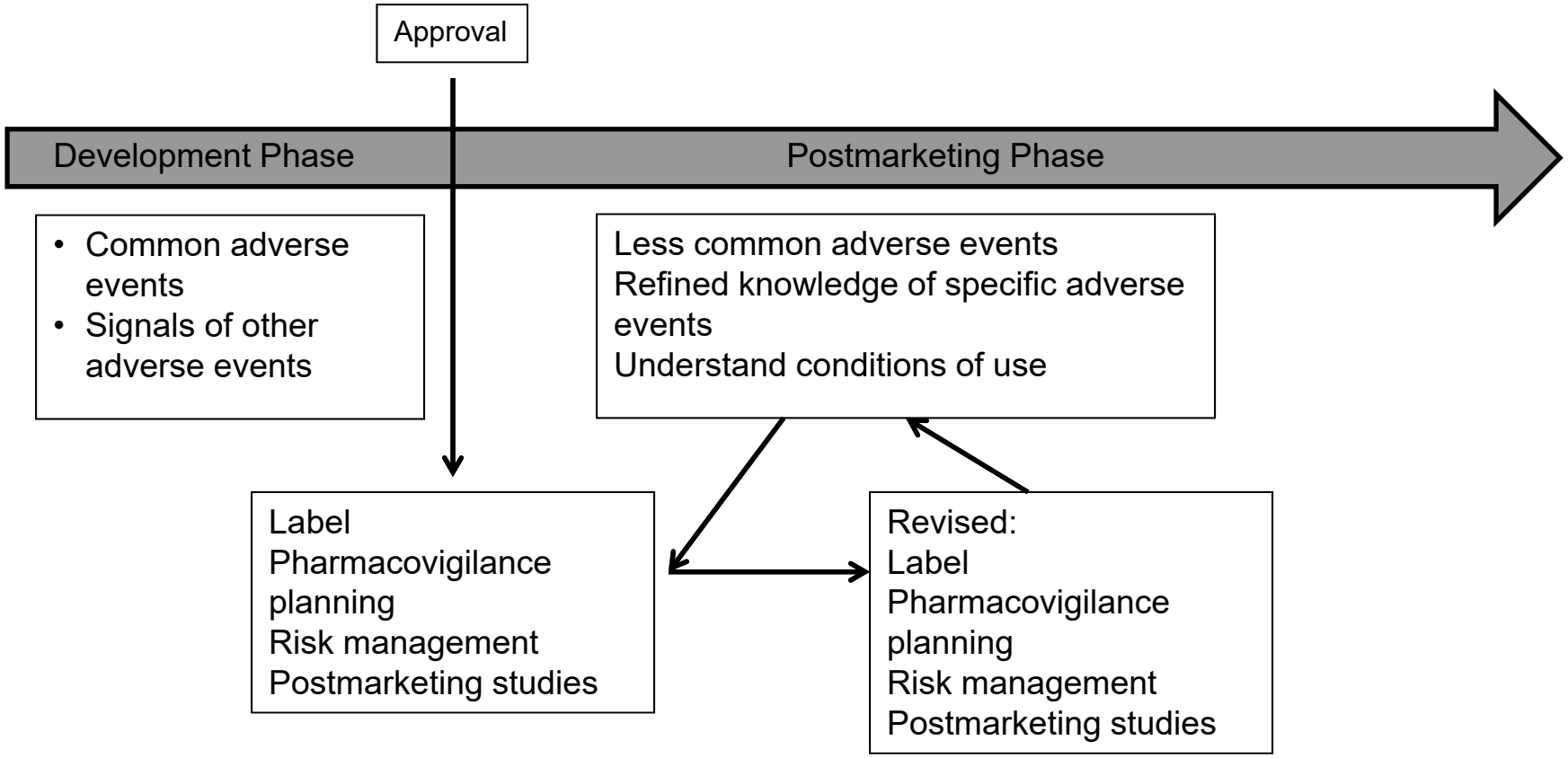
Pharmacovigilance

- The science and activities related to the detection, assessment, understanding, and prevention of drug-related problems (WHO).

- **Conducted across a medicine's life-cycle**
  - Premarketing
  - Post-Marketing



Drug safety knowledge is accrued throughout the lifecycle of a drug



- **Regulatory requirements**
- **WHO-Prequalification (PQ) requirement**
- **Prevention and treatment guidelines**
- **Related terminology**:
  - Safety surveillance
  - Pharmacoepidemiology
  - Postmarketing surveillance
  - Phase IV studies

Who Needs Safety Information?

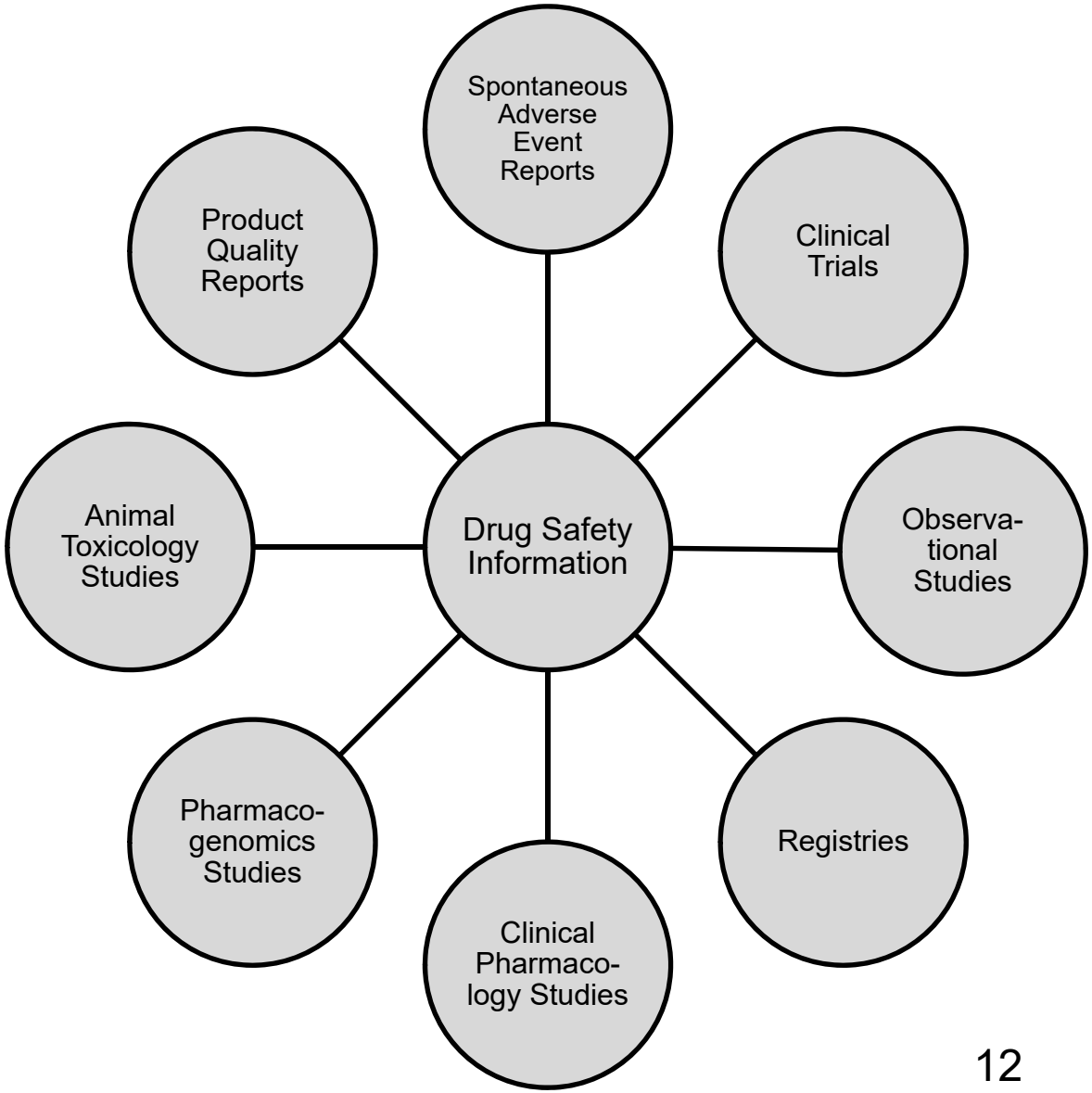
Health Regulators and Other Authorities:

1. Approval and availability of medicines
2. Rational use
3. Treatment and prevention guidelines
4. Monitor quality

Health care providers

Patients

Sources of Safety Information



Medicines are among the most important health interventions

- Rx-Related “Best Buys” in Health:
  - Vaccinate children
  - Prevent and treat childhood pneumonia, diarrhea, and malaria
  - Attack the spread of HIV, including providing antiretroviral medications
  - Treat TB patients

Disease Control Priorities Project, www.dcp2.org

Why Pharmacovigilance?

- Safety information collected during drug and vaccine development is *incomplete*:
  - Animal tests insufficient to predict human safety
  - Clinical trials evaluate limited duration and numbers of carefully selected patients in carefully selected settings
  - Pregnant women and other vulnerable groups typically excluded

THE LANCET

The Lancet, Volume 278, Issue 7216, Page 1358, 16 December 1961
doi:10.1016/S0140-6736(61)90927-8

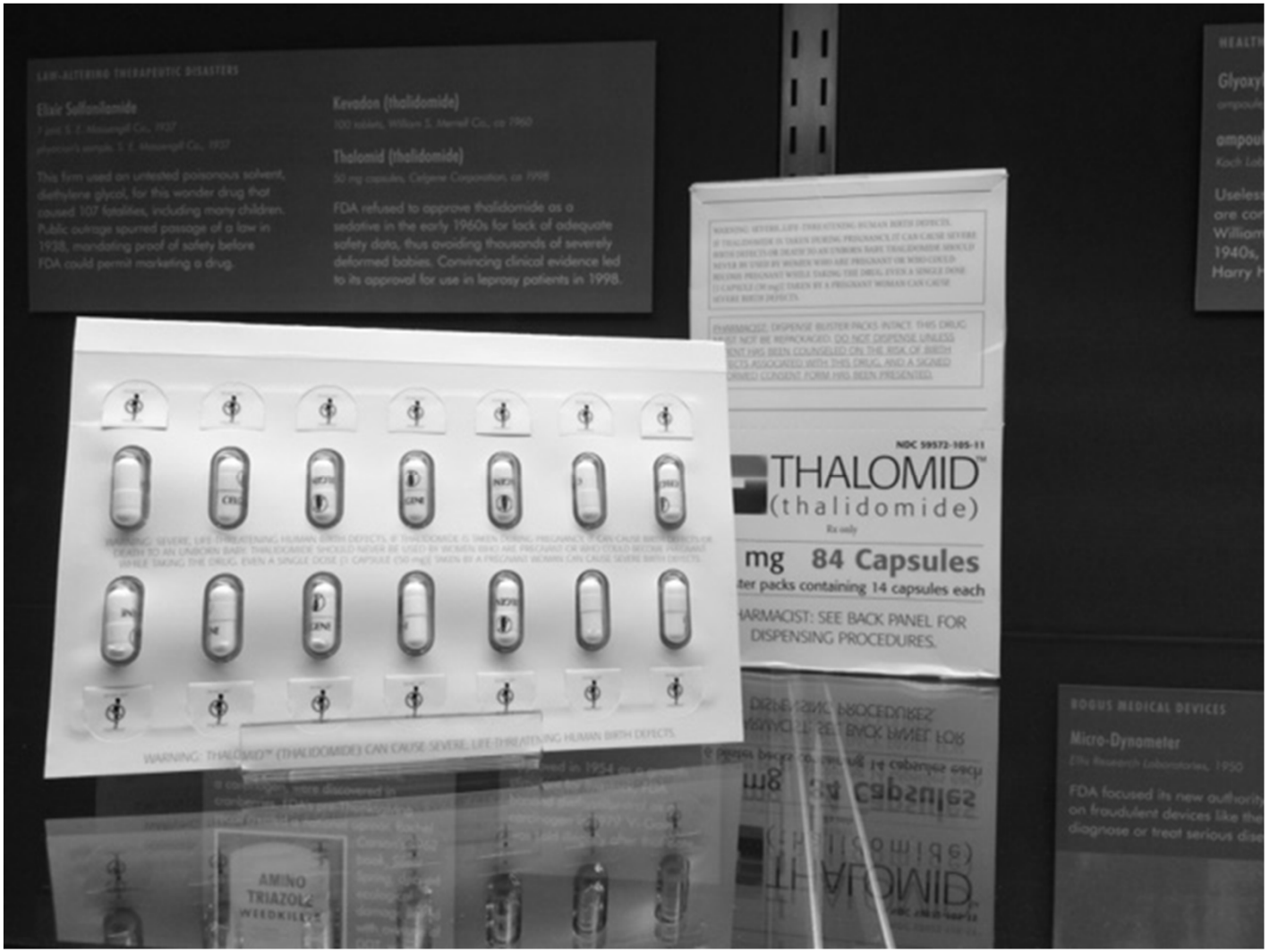
THALIDOMIDE AND CONGENITAL ABNORMALITIES

W.G. Mcbride

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed


LAW-ALTERING THERAPEUTIC DISASTERS
Elixir Sulfanilamide
This firm used an untested poisonous solvent, diethylene glycol, for this wonder drug that caused 107 fatalities, including many children. Public outrage spurred passage of a law in 1938, mandating proof of safety before FDA could permit marketing a drug.
Kevadon (thalidomide)
Thalomid (thalidomide)
FDA refused to approve thalidomide as a sedative in the early 1960s for lack of adequate safety data, thus avoiding thousands of severely deformed babies. Convincing clinical evidence led to its approval for use in leprosy patients in 1998.
NDC 59572-105-11
THALOMID™
(thalidomide)
Rx only
mg 84 Capsules
ter packs containing 14 capsules each
HARMACIST: SEE BACK PANEL FOR
DISPENSING PROCEDURES.
WARNING: THALOMID™ (THALIDOMIDE) CAN CAUSE SEVERE, LIFE-DISABLING HUMAN BIRTH DEFECTS.
AMINO
TRIAZOL
ROGUS MEDICAL DEVICES
Micro-Dynometer
FDA focused its new authority
on fraudulent devices like the
diagnose or treat serious dise

Why be concerned about adverse drug reactions?

- People in every country of the world are affected by adverse drug reactions (ADRs)
  - ADRs are among a leading cause of death
  - At least 60% of ADRs are believed to be preventable
- In some countries ADR-related costs, such as hospitalization, surgery and lost productivity, exceed the cost of medications
  - Countries may spend 15-20% of their hospital budget managing drug complications
  - In the United States, drug-related morbidity and mortality has been estimated to cost between USD 30.1 billion and USD 136.8 billion

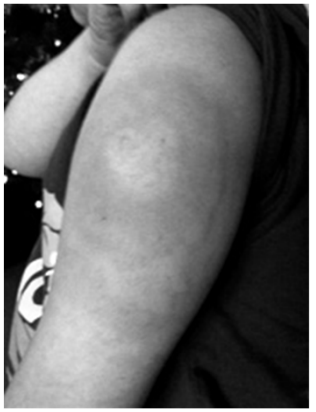
Safety Requirements for Medicines

- No medicine is absolutely safe
- “Safety” = benefits exceed risks for defined population and use
- Determination of safety is inseparable from consideration of the medicine’s effectiveness

Pharmacovigilance at the local, national , and international level

Local Level: Example

- Patient seeks care for adverse event
- Clinician recognizes it as a potential adverse event following immunization (AEFI)
- AEFI is recorded and reported



National Level: Roles of the Drug Regulator

Access to medicines

- Assess efficacy, safety, quality

Protection of the public

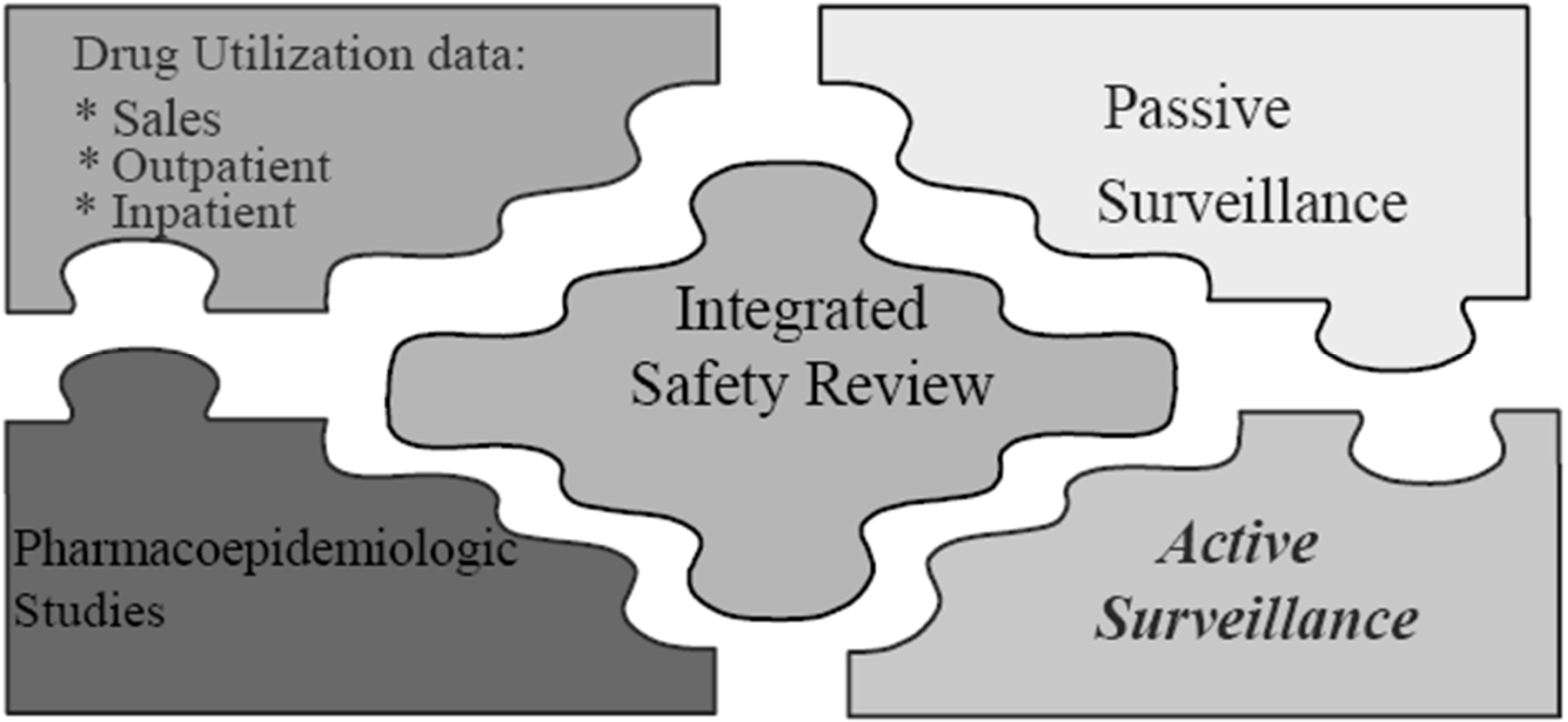
- During clinical trials
- Postapproval

Information to the public

National Level – *More Specifically*

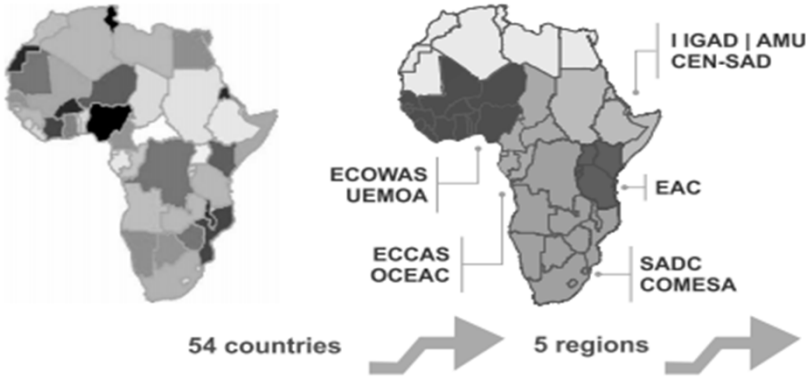
- Feedback to reporter including eliciting further follow-up information
- Code & enter adverse event reports into data base
- Causality assessment
- Investigation
- Identify potential safety signals
- Evaluate signals
- Assessment of benefit-risk
- Collaborates with public health programs
- Communication

Components of Postmarketing Surveillance at the US FDA



Regional Level

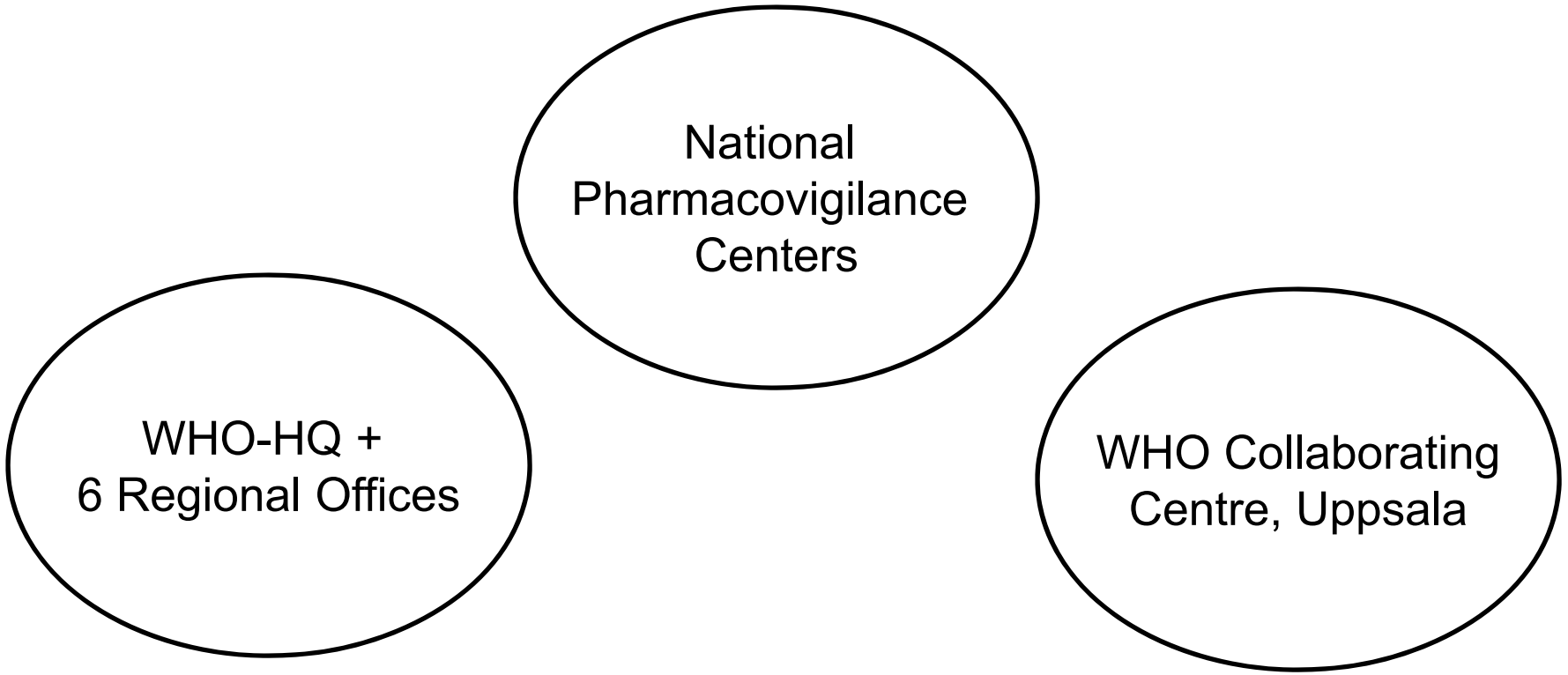
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- Asia-Pacific Economic Cooperation (APEC)
- African Medicines Regulatory Harmonization Initiative of the African Union's New Partnership for Africa's Development (NEPAD)



International Level

- Technical assistance
- Normative & policy
- Signal detection
- Signal evaluation
- Funding
- Capacity building/training
- Coordination/communication
- Research

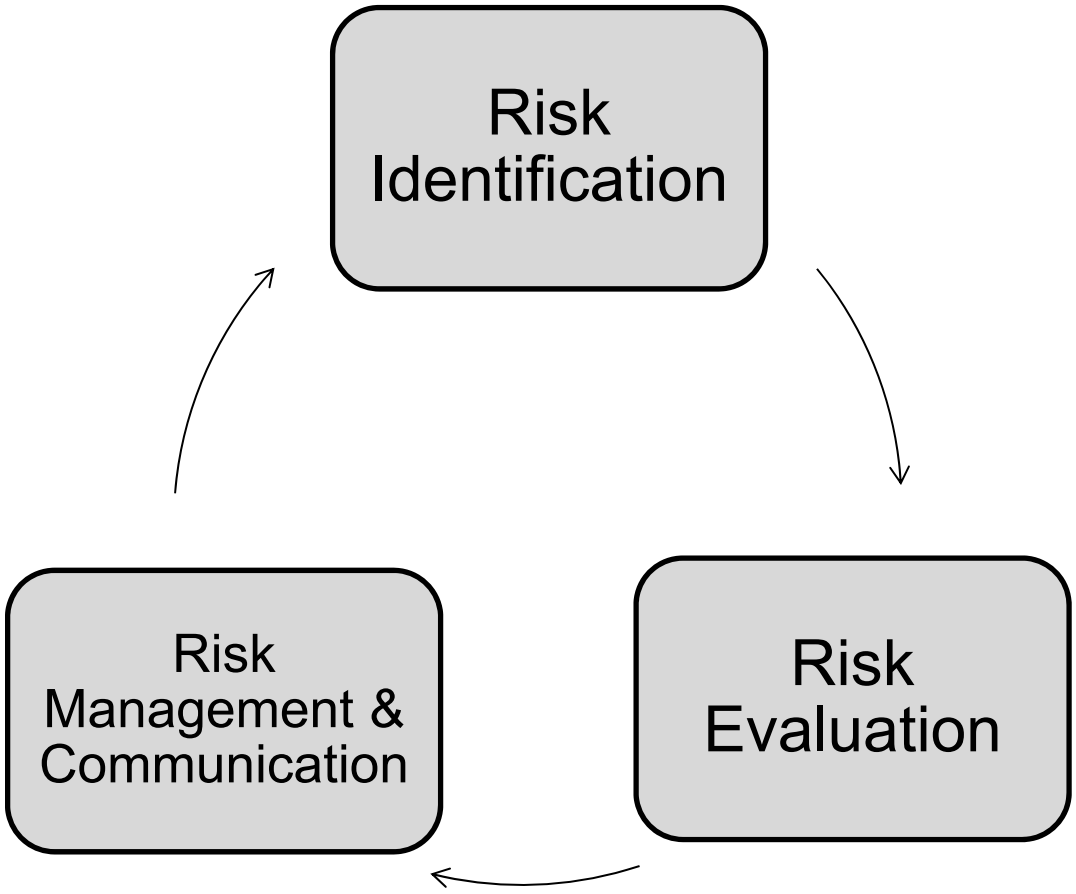
WHO Program for International Drug Monitoring



WHO Program for International Drug Monitoring

- Full Member Countries (134)
- Associate Member Countries (29)
- WHO Collaborating Centers

The Pharmacovigilance Process



1. Risk Identification

- Purpose:
  - Identify suspected side effects

- Sources:
  - Spontaneous adverse event case reports
  - Premarketing studies: preclinical and clinical trials
  - Medical literature
  - Bulletins from other regulatory agencies

Adverse Events of Particular Interest

- Serious adverse event (SAE)
- Serious and unexpected serious adverse reaction (SUSAR)
- Adverse events following introduction of new medicines
- Adverse events following changes in treatment guidelines

Definitions

Adverse Drug Reaction (ADR)

- Any untoward and unintended responses to an investigational medicinal product **related** to any dose administered

Definitions

- ***Unexpected*** Adverse Drug Reaction
  - Unexpected adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s).
    - e.g. investigator's brochure or summary of product characteristics

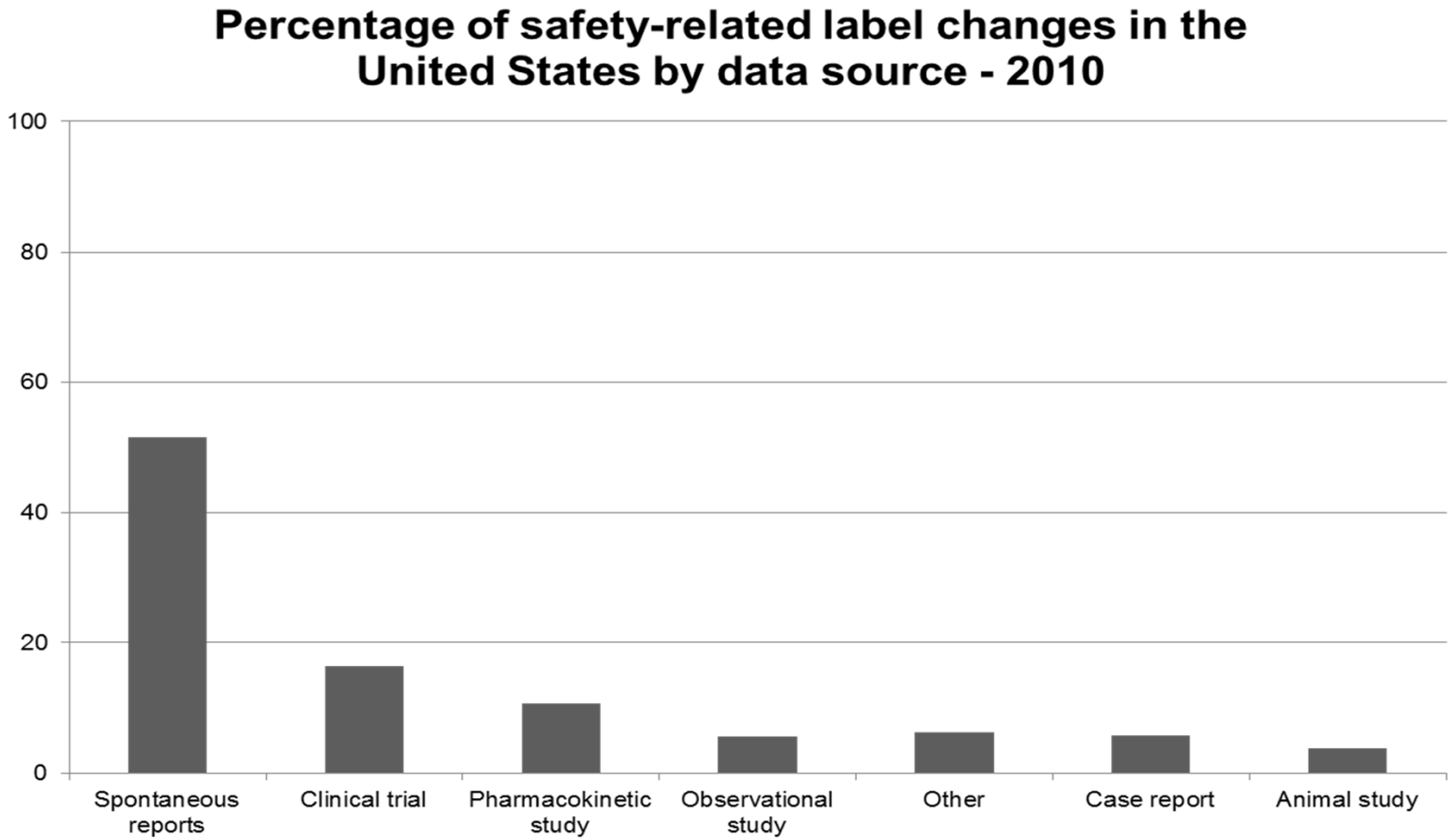
Definitions

- **Serious adverse event (SAE)** or reaction is any untoward medical occurrence that at any dose:
  - Results in death,
  - Is life-threatening,
  - Requires inpatient hospitalization or prolongation of existing hospitalization,
  - Results in persistent or significant disability/incapacity, or
  - Is a congenital anomaly/birth defect.

Spontaneous Adverse Drug Reaction Reporting

- Voluntary, passive reporting of suspected adverse events during routine clinical practice
- Advantages:
  - Can be nation-wide, generate signals
  - Examples: lipodistrophy, lactic acidosis, nephrotoxicity
  - Characterize at-risk groups, risk factors, and clinical characteristics through case series
- Disadvantages:
  - Underreporting, recognition problems, biases, no denominator, report quality issues

Spontaneous Reports are Important



Source: Lester et al. Evaluation of FDA safety-related drug label changes in 2010. Pharmacoepi Drug Safety 2013;22:302-5.

Strengthening Spontaneous Reporting

1. Define priorities for reporting
2. Easy contact with and quick access to pharmacovigilance system
3. Information and support for reporting suspected ADRs
4. Feedback on pharmacovigilance activities
5. Training
6. Quality assurance visits
7. Ongoing presence of focal persons

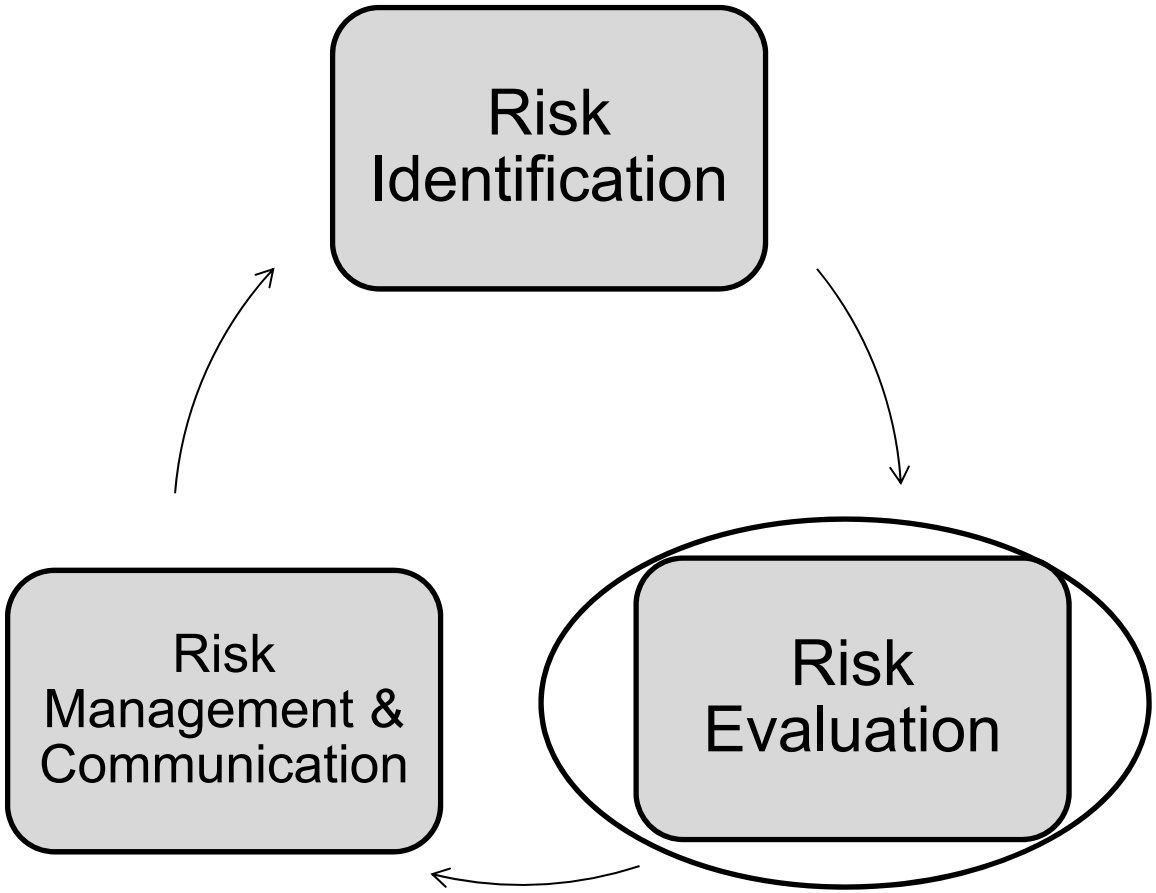
Spontaneous Adverse Drug Reaction Reporting in Rural Districts of Mozambique

Esperança Sevene,[1] *Alda Mariano,*[1] *Ushma Mehta,*[2] *Maria Machai,*[3] *Alexander Dodoo,*[4] *David Vilardell,*[5] *Sam Patel,*[1] *Karen Barnes*[2] and *Xavier Carné*[5]

1 Eduardo Mondlane University Medical School, CIMed, Maputo, Mozambique
2 Division of Clinical Pharmacology, University of Cape Town Medical School, Cape Town, South Africa
3 Ministry of Health, Maputo, Mozambique
4 University of Ghana Medical School, Accra, Ghana
5 Clinical Pharmacology Service, Hospital Clinic and IDIBAPS, Barcelona, Spain

Sevene et al. Drug Safety 2008;31:867-876

The Pharmacovigilance Process



2. Risk Evaluation

- **Qualitative**: Causality assessment. Determine whether there is reasonable possibility that the product is etiologically related to the adverse experience

- **Quantitative**: Use epidemiological methods to confirm and quantify the relationship between the drug and the ADR

Qualitative: Causality Assessment

- Determine whether there is reasonable possibility that the product is etiologically related to the adverse experience

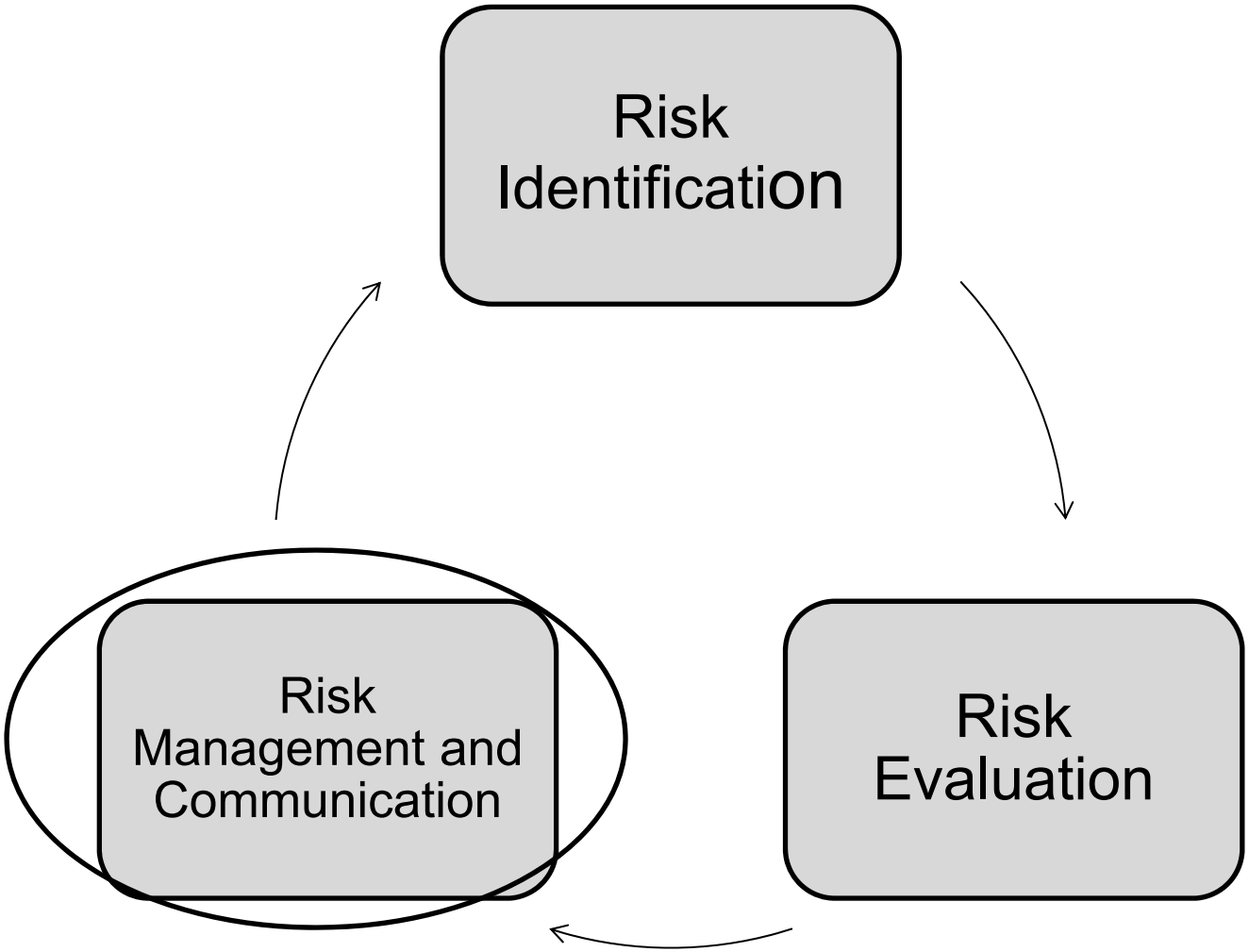
Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

Quantitative

Use epidemiological methods to confirm and quantify the relationship between the drug and the adverse event:

- Registries,
- Cohort studies
- Case-control studies
- Phase IV, and other studies

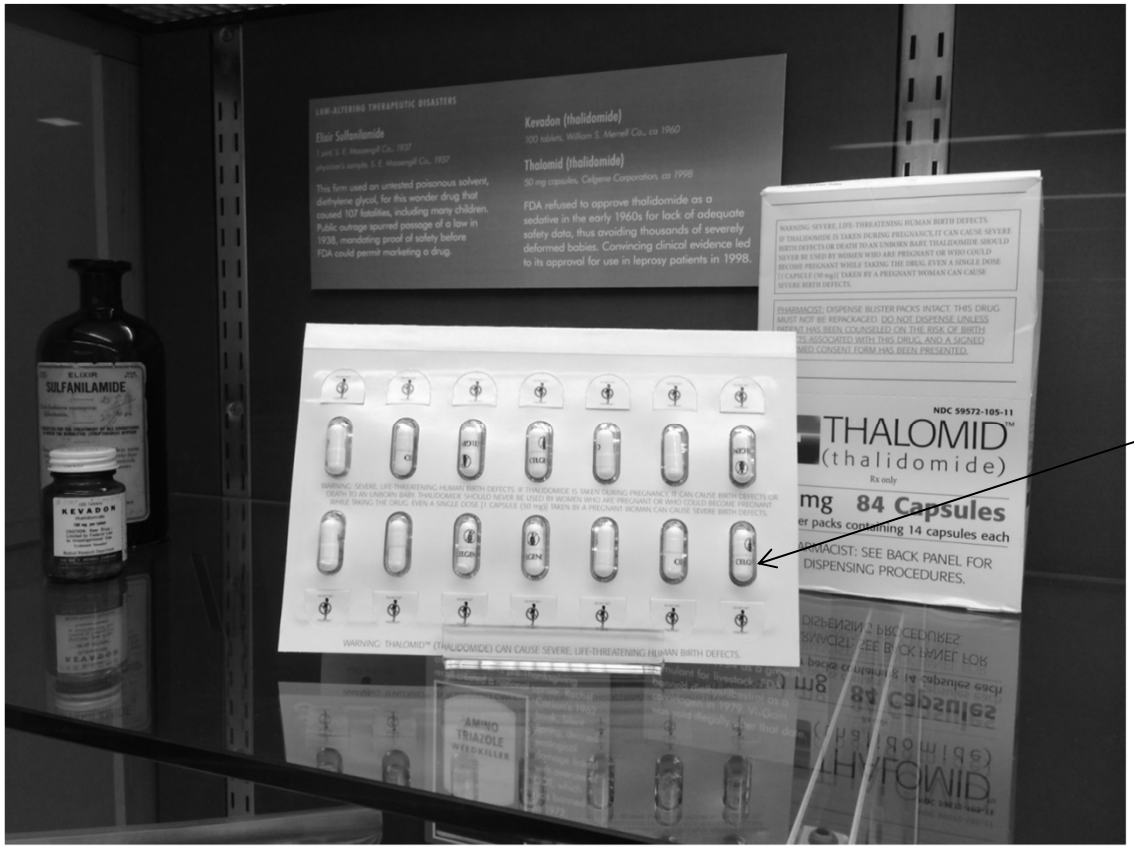
Pharmacovigilance Process



Available Tools for Risk Management

1. Product labeling
2. Education and outreach
3. Reminder/prompting systems
4. Restricted distribution
5. Suspend procurement
6. Withdraw product from local approved or essential medicines list

Example of a Reminder: Isotretinoin (Accutane)

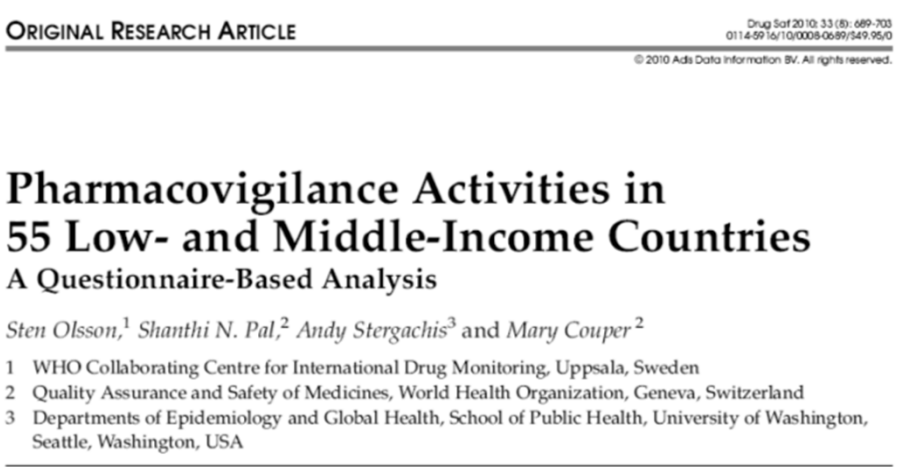


Risk Management Goal and Approach: Examples

Medicine	Goal	Approach
Clozapine	No agranulocytosis	WBC monitoring
Thalidomide	No fetal exposure	Pregnancy prevention and monitoring for pregnancy
Isotretinoin	No fetal exposure	Pregnancy prevention and monitoring for pregnancy ▪Registration and education of patients, pharmacists, prescribers, distributors ▪Packaging & Reporting system ▪Limited supplies ▪Pregnancy tests

Gaps in PV in LMICs

- Infrastructure, resources, training, and methodologies
- Low number of ADR reports for signal detection
- Limited active surveillance
- Few countries allocate budgets to PV, but some public health programs and donor organizations supporting PV activities



ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (8): 689-703
0114-5916/10/0008-0689/$49.95/0

Pharmacovigilance Activities in 55 Low- and Middle-Income Countries

A Questionnaire-Based Analysis

Sten Olsson,[1] *Shanthi N. Pal,*[2] *Andy Stergachis*[3] and *Mary Couper*[2]

1 WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
2 Quality Assurance and Safety of Medicines, World Health Organization, Geneva, Switzerland
3 Departments of Epidemiology and Global Health, School of Public Health, University of Washington, Seattle, Washington, USA

http://apps.who.int/medicinedocs/documents/s19152en/s19152en.pdf

Kuemmerle *et al. Malaria Journal* 2011, **10**:57
http://www.malariajournal.com/content/10/1/57

MALARIA JOURNAL

RESEARCH **Open Access**

Assessment of global reporting of adverse drug reactions for anti-malarials, including artemisinin-based combination therapy, to the WHO Programme for International Drug Monitoring

Andrea Kuemmerle[1,2,3], Alex NO Dodoo[4], Sten Olsson[5], Jan Van Erps[6], Christian Burri[1,2], Paul S Lalvani[7*]

- Malaria-endemic countries submitted only 1.2% of all of the ADR reports
- Only 60 out of 21,312 ADR reports were related to ACTs, 51 of which were coming from four sub-Saharan African countries.

Drug Saf (2016) 39:335–345
DOI 10.1007/s40264-015-0387-4

ORIGINAL RESEARCH ARTICLE

Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®

Haggar H. Ampadu[1,2] · Jarno Hoekman[2] · Marieke L. de Bruin[2] · Shanthi N. Pal[3] · Sten Olsson[4] · Daniele Sartori[4] · Hubert G. M. Leufkens[2] · Alexander N. O. Dodoo[1]

Key Points

As at the end of September 2015, 35 African countries were Full Members of the WHO Programme for International Drug Monitoring.

The 35 countries from Africa have submitted 103,499 (0.88 %) of the global total of 11,824,804 ICSRs in VigiBase® submitted by all 122 members of the PIDM.

ICSRs from Africa differ from the rest of the world in relation to the classes of products implicated and the age of patients.

Top 10 product classes in African reports vs rest of world (RoW)

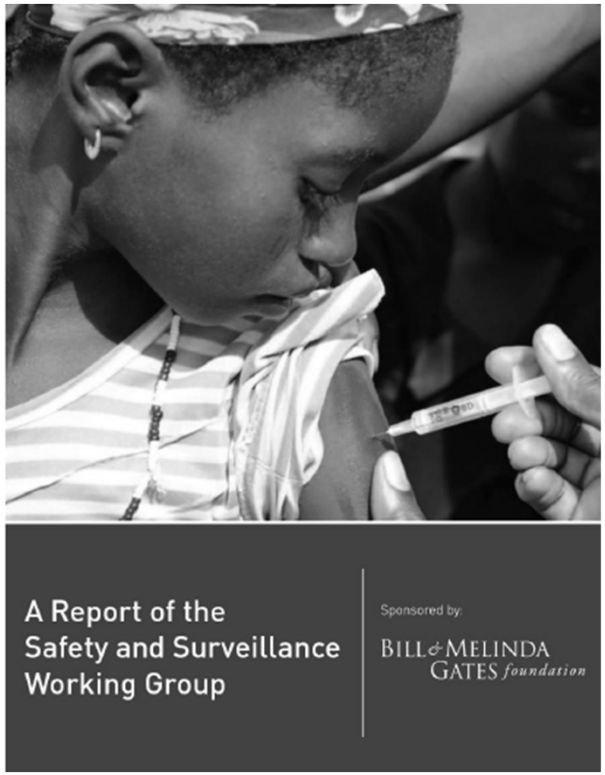
ATC code	Africa (%)[a]	RoW (%)[b]
J05AF—nucleoside and nucleotide reverse transcriptase inhibitors	14,530 (14.04)	44,055 (0.38)
J05AG—non-nucleoside reverse transcriptase inhibitors	9407 (9.09)	26,107 (0.22)
J05AR—antivirals for the treatment of HIV infections, combinations	5692 (5.50)	34,927 (0.30)
J01EE—combinations of sulfonamides and trimethoprim, incl. derivatives	3082 (2.98)	81,206 (0.69)
C09AA—ACE inhibitors, plain	2503 (2.42)	154,176 (1.32)
S01AA—antibiotics	2340 (2.26)	179,635 (1.53)
J07AH—meningococcal vaccines	2308 (2.23)	48,480 (0.41)
L03AB—interferons	2130 (2.06)	211,098 (1.80)
J04AM—combinations of drugs for treatment of tuberculosis	1933 (1.87)	7043 (0.06)
D06AX—other antibiotics for topical use	1855 (1.79)	103,228 (0.88)

RoW rest of the world, *ATC* anatomic therapeutic chemical, *ACE* angiotensin-converting enzyme, *ICSRs* individual case safety reports

[a] Percentage includes all African ICSRs ($n = 103{,}499$) in VigiBase® (excluding Swaziland, $n = 27$)

[b] Percentage of all RoW ICSRs ($n = 11{,}721{,}305$) in VigiBase®

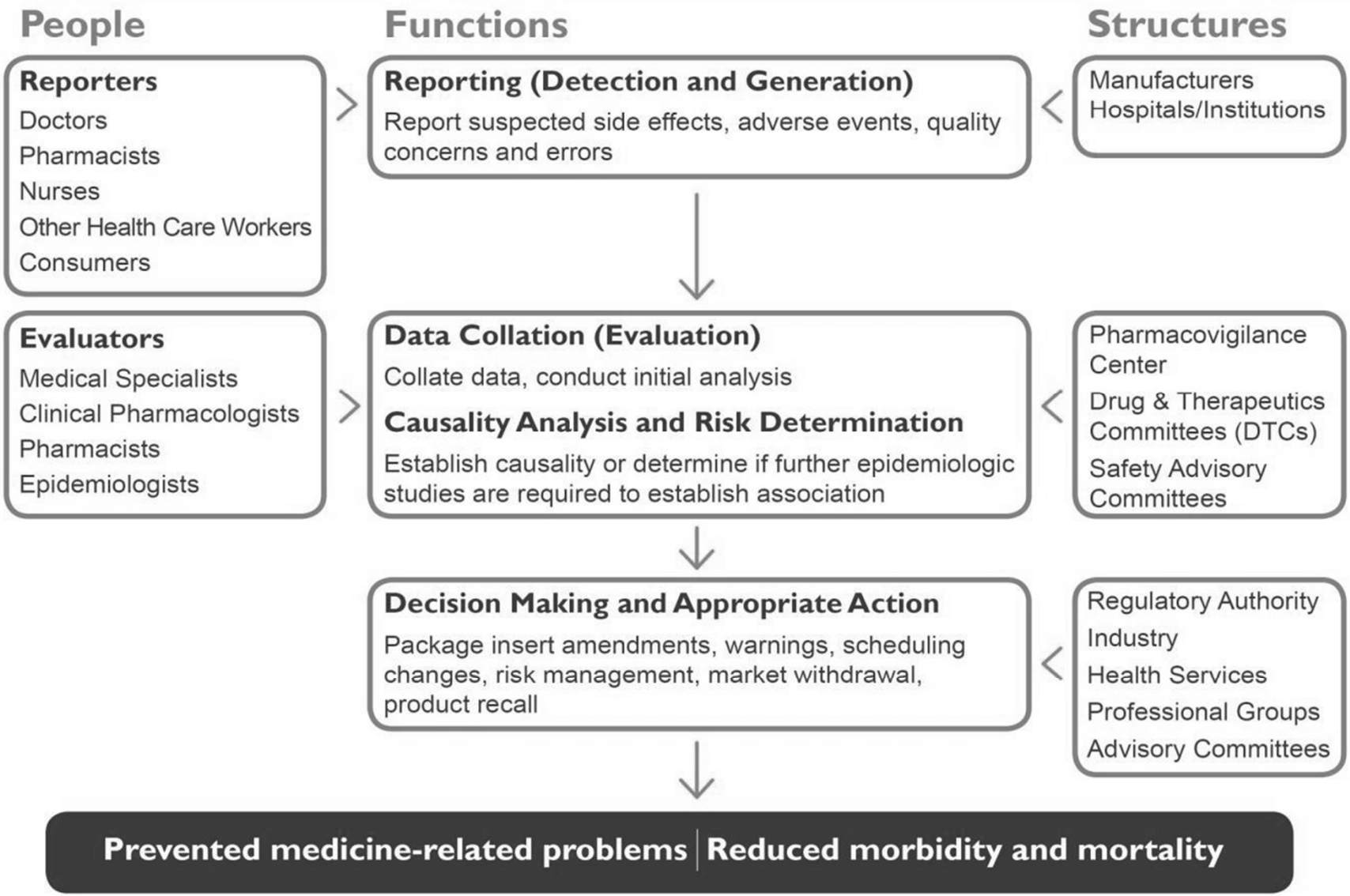
Ampaudu, et al (2006)



- “Drugs and vaccines are reaching unprecedented numbers of people in low- and middle-income countries.
- These products have tremendous potential to save lives and reduce suffering, but many of the countries in which these products will be used do not have the capacity to effectively monitor their post-market safety.”

https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%2011%2019%2013_designed.pdf

The Pharmacovigilance Framework



Summary

- Pharmacovigilance of marketed medicines is part of a continuum: Benefit-Risk
- Both clinical trials safety and post-marketing pharmacovigilance are critical throughout a medicine's life-cycle.
- Pharmacovigilance identifies and quantifies important adverse events and provides vital information for the rational and safe use of medicines

"Ensuring the acceptability of the risk–benefit profile of a drug after it is approved… is no less central a public health mission than ensuring the acceptability of the profile before it is permitted to enter the market."

Thank You

stergach@uw.edu
www.globalmedicines.org