# INTRODUCTION TO PHARMACOVIGILANCE CONCEPTS AND GENERAL FRAMEWORK

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## Pharmacovigilance (Drug Safety)

- Pharmakon (=drug) and vigilare (=keep watch).
- *Discipline* and activities relating to the **detection, assessment, understanding and prevention *& management* of adverse effects** or any other drug-related problem

(WHO, 2002)

## Pharmacovigilance. Aims

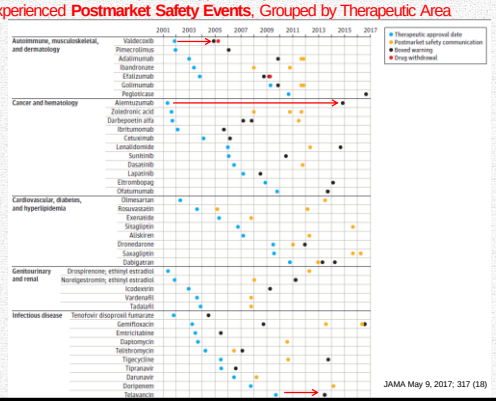
- **Early detection** of unknown safety problems
- Identification of **risk factors**
- **Quantification** of risks
- **Preventing** patients from being affected unnecessarily

Rational and Safe Use of Medicines, WHO

## Why is Pharmacovigilance Important?

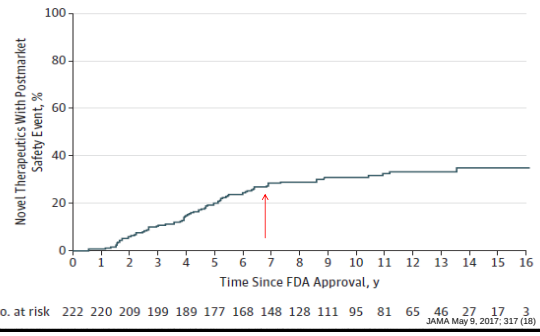
- Adverse Drug Reactions are among the top ten causes of mortality (Lazarou J. et al., 1998)
- The percentage of hospital admissions due to drug related events in some countries is about or more than 10% (Bhalla et al, 2003; Imbs et al, 1999)
- Drug related morbidity and mortality expenses exceeded US$ 177.4 billion in the USA in 2000 (Ernst & Grizzle, 2001)

## Timeline of Novel Therapeutics Approved by the US FDA, 2001-2010, That Experienced **Postmarket Safety Events**, Grouped by Therapeutic Area



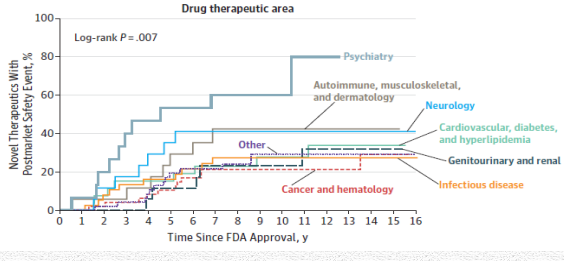

JAMA May 9, 2017; 317 (18)

## Proportion of **Novel Therapeutics** Approved by the US Food and Drug Administration (FDA) from 2001 through 2010 affected by any Postmarket Safety Event as of February 2017




JAMA May 9, 2017; 317 (18)

## Proportion of Novel Therapeutics Approved by the US Food and Drug Administration (FDA) From 2001 Through 2010 Affected by Any Postmarket Safety Event by Therapeutic Area




JAMA May 9, 2017; 317 (18)

## Phases of Drug Development

STUDIES IN VITRO AND IN VIVO

ANIMAL TESTING
- •SHORT TERM
- •LONG TERM

Questions answered in this phase
- • Is the substance biologically active?
- • Is it safe?

**PHASE I**

Who? Healthy volunteers, small number

Why? Safety, biological effects, pharmacokinetics profile, dosage range, duration of action and drug interactions

By Whom? Clinical Pharmacologists

**PHASE II**

Who? Selected patients (up to 300 patients)

Why? Therapeutic efficacy, dose range, kinetics, metabolism

By Whom? Clinical pharmacologists, clinical investigators

**PHASE III**

Who? Large sample of selected patients (500-3000 patients)

Why? Safety and efficacy

By Whom? Clinical pharmacologists, clinical investigators and pharmacoepidemiologists

**PHASE IV**

Who? Patients given drug for therapy

Why? Adverse reactions-labeling changes, patterns of drug utilization, additional indications discovered, pricing negotiations, marketing

By Whom? Pharmacoepidemiologists and all physicians

Areas:

Pharmacovigilance

Pharmacoeconomics

| 1-5 years (μ=2.6 yr) | 2-10 years (μ=5.6 yr) | Variable |
|---|---|---|
| *Preclinical* | *Clinical* | *Postmarketing Surveillance* |

Kaitlin KI, et al. J Clin Pharmacol 1987;27:542-548; Young FE, et al. JAMA1988; 259:2267-2270

| Preclinical | Phase 1 | Phase 2 | Phase 3 | APPROVAL | Postmarketing |
|---|---|---|---|---|---|
| Safety & Biological Activity | Safety & Dosage | Safety & Efficacy | Safety & Efficacy | | Safety Surveillance |
| SAFETY CONCERNS | | | | | |

## Limitations of Clinical Trials

- Trial population
  - Size (small ~ 3,000 subjects)
  - Representativeness of trial population vs. real world population
  - Trial population vs. real world or treated population (CT: narrowly defined study population: age groups, comorbidities, concomitant medications)
- Indications for use
  - Proposed indication for use
    - Patients at complex disease stages often not enrolled
- Duration of trial
  - Typical chronic use (years) vs. trial (several weeks to months)
- Frequency of ADRs
  - Uncommon ADRSs are difficult to detect

FDA, 2018; Ann Intern Med. 2010;153:600-606.

## Sample Size

Statistical Power

| Frequency (AE) | 95% | 90% | 80% | 63% |
|---|---|---|---|---|
| 1/100 | 300 | 231 | 161 | 100 |
| 1/500 | 1500 | 1152 | 805 | 500 |
| 1/1000 | 3000 | 2303 | 1,610 | 1000 |
| 1/5000 | 15,000 | 11,513 | 8,048 | 5000 |
| 1/10,000 | 30,000 | 23,026 | 16,095 | 10,000 |
| 1/50,000 | 150,000 | 115,130 | 80,472 | 50,000 |

Probability of detecting an unintended drug effect if it really occurs in the population under study.

Sackett DL, 1986. In: Inman WHW, Monitoring for drug safety 1986: 471-483.



## Ideally, a medication should be prescribed to:

- The **right patient**,
- With the **right disease**,
- With the **right medication**,
- In the **proper dosage and intervals**,
- And for the **appropriate length of time**

## Pharmacovigilance & Drug Utilization

- It is not always the product that determines drug safety but **how it is used**
- There is a high risk of misuse of drugs
  - Disease
  - Population
  - Drug
  - Health care system
- More than 50% of ADRs are preventable

## Public Health Programs and Pharmacovigilance

- Incidence and prevalence of the disease
- Morbidity and mortality rates
- Number of patients treated
- Number of drug units delivered

What about **the risk / effectiveness** of drugs used?

## IMPORTANT DEFINITIONS IN PHARMACOVIGILANCE

## Side Effects

- Any **unintended outcome (negative or positive effects)** that seems to be associated with treatment.
- This term is often used in **patient information** and other contexts.
- Unintended effect occurring at normal dose related to the pharmacological properties?

## Adverse Effect

A **negative or harmful patient <u>outcome</u>** that <u>seems to be associated</u> with treatment, including there being no effect at all

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/.

## Adverse Event

- Any **<u>unfavorable and unintended sign</u>** (including an abnormal laboratory finding, for example), **symptom, or disease <u>temporally</u> associated with the use of a medicinal product, <u>but not necessarily causally related</u>**
- Unexpected medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and where **not necessarily have a casa relationship with the treatment.**

ICH E2A Guideline: 'Clinical Data Management: Definition and the Standards for Expedited Reporting', FDA guidance,

## Adverse Event

| Severity (Intensity) | Seriousness | Expectedness | Listedness | Causality |
|---|---|---|---|---|
| • Mild<br>• Moderate<br>• Severe | • Serious<br>• Non-serious | • Expected<br>• Unexpected<br>*Reference Safety Information of IB (Development), Label (Marketed)* | • Listed<br>• No listed<br>*Label* | • Related<br>• No related (unrelated) |

## Adverse Drug Reaction (ADR)

- A harmful effect suspected to be **<u>caused by a drug</u>**
- A response to a drug which is **noxious and unintended**, and which occurs at **doses normally used in man** for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function (WHO, 1972)

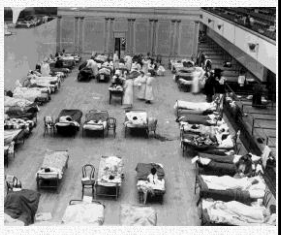
| Standard Categories of Frequency | |
|---|---|
| Very common | ≥ 1/10 [≥ 10%] |
| Common | ≥ 1/100 to < 1/10 [≥ 1% and < 10%] |
| Uncommon | ≥ 1/1000 to < 1/100 [≥ 0.1% and < 1%] |
| Rare | ≥ 1/10,000 to < 1/1000 [≥ 0.01% and < 0.1%] |
| Very rare | < 1/10,000 [< 0.01%] |
| Frequency not known* | Cannot be estimated from the available data |

* Summary of Product Characteristics (SmPC)/QRD guidelines recommends language "Not known", CDS recommends language "Frequency not known".

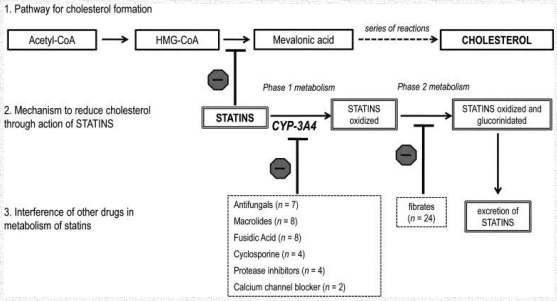
CIOMS III/IV convention and the European Commission document "A Guideline on Summary of Product Characteristics" dated September 2009. https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/.

## Are ADRs the Same within a Therapeutic Class?

- Variation in terms of:
  - Severity
  - Likelihood of occurrence
  - Effect on individual patients
  - Public health impact

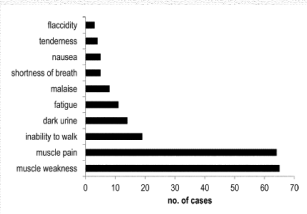


## Example




Physiotherapy Canada 2014; 66(2);124–132

## Key Characteristics of Fatal Cases of Statin-Induced Rhabdomyolysis (n=17)




| Characteristic | No. of cases |
|---|---|
| Age, y | |
| ≤45 | 2 |
| 46–65 | 5 |
| 66–75 | 7 |
| >75 | 3 |
| Sex | |
| Male | 15 |
| Female | 2 |
| Pre-existing conditions | |
| Cardiovascular disease | 13 |
| Diabetes mellitus | 10 |
| Renal impairment | 7 |
| Dyslipidemia | 5 |
| Time to onset, d | |
| ≤7 | 5 |
| 8–14 | 4 |
| ≥15 | 2 |
| Not reported | 6 |
| Type of statin | |
| Simvastatin | 6 |
| Atorvastatin | 6 |
| Lovastatin | 3 |
| Cerivastatin | 1 |
| Fluvastatin | 1 |
| Statin dose, mg | |
| ≤20 | 5 |
| 21–39 | 3 |
| ≥40 | 4 |
| Not reported | 5 |
| Concomitant drugs | |
| Antibiotics | 6 |
| Fibrates | 2 |
| Antifungals | 1 |
| Other | 4 |
| None | 4 |

Physiotherapy Canada 2014; 66(2);124–132

## **Serious** Adverse Experience, Event or Reaction

- Results in any of these outcomes:
  - **Death**
  - **Life-threatening** adverse experience
  - Inpatient **hospitalization** –new or prolonged
  - Persistent/significant **disability/incapacity**
  - **Congenital birth defect**
  - Other serious: based upon appropriate **medical judgment**, they may jeopardize the patient and require intervention to prevent a serious outcome

  Note: Seriousness is different to **severity**, which refers to the **intensity** of the event (e.g. severe headache)

Federal Register -Code of Federal Regulations. 21 CFR 314.80 (a), FDA 2018

## Unexpected Adverse Reaction

- Not consistent with applicable product information or characteristics of drug

## Exercise

- Relate each case with each definition using the list distributed during the session

| Cases | Relate w/correct answer |
|---|---|
| 1) Female patient who experienced increased of hepatic enzymes after one week on an antifungal medication | a) Adverse event |
| 2) This is a 35 year-old male, soccer player, who complained of myalgias and was on antihypertensive drugs and lipid lowering medications | b) Expected adverse drug reaction |
| 3) This is a 49 year-old female patient exposed to insulin who experienced headache, dizziness and syncope and recovered after drinking a glass of orange juice | c) Adverse drug reaction |

## Benefit, Benefit/Risk

- Benefit:
  - Positive therapeutic effects of treatment in an individual
  - Positive health, social or psychological effects of treatment from the patient's perspective.
- Benefit-risk: Description of both positive and negative effects of a medicine and the likelihood of their occurrence, as far as they are known, as perceived by an individual.
  - B/R represents a critical information that health professionals and patients need to make wise therapeutic decisions. The perspectives of professionals and patients on the issues may differ.

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/.

## Effectiveness, Effectiveness/Risk, Efficacy

- Effectiveness: A measure of the chances or odds (probability) of a medicine working positively as expected for patients.
  - Measure of the effect of a drug in the "real world"
- Effectiveness-risk: A comparison of the statistical chances (probability) of a medicine working as expected and/or causing harm.
- Efficacy: A measure of the extent to which a chemical substance or medicine works positively under laboratory conditions and in a selected group of patients.

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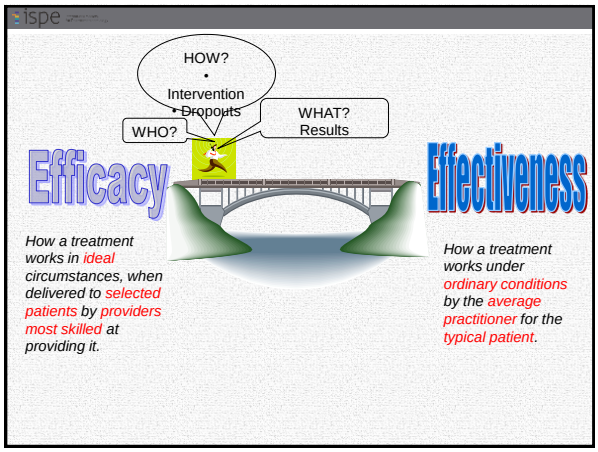
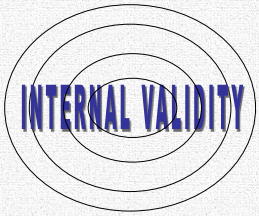



## Efficacy: Randomized Controlled Clinical Trials

- Rigorous inclusion and exclusion criteria:
  - Limited to certain study population
  - Limited to a spectrum of a disease
  - Limited to certain number of comorbid conditions
  - Limited to certain number of medications




## Effectiveness

- Heterogeneous group of patients:
  - Age
  - Gender
  - SES
- Co-morbid conditions
- Multiple treatments (pharmacologic and non pharmacologic treatments)
- Variation of patient adherence to treatment
- Variation of medical practice and compliance to guidelines
- Variation of medical knowledge among patients
- Access to care (HCS), type of care
- Costs

EXTERNAL VALIDITY

## Harm, Hazard and Risk

- Harm: The damage, injury or impairment that is or might be caused by a medicine, including death.
- Hazard: The intrinsic chemical or biological characteristics of a medicine or its use that have the potential to cause harm.
- Risk: The statistical probability of harm being caused.

Doxorubicin ⟶ Cardiotoxicity ⟶ Cardioversion

(hazard) (harm)

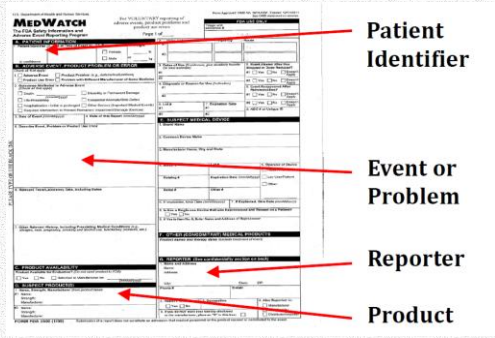
https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/

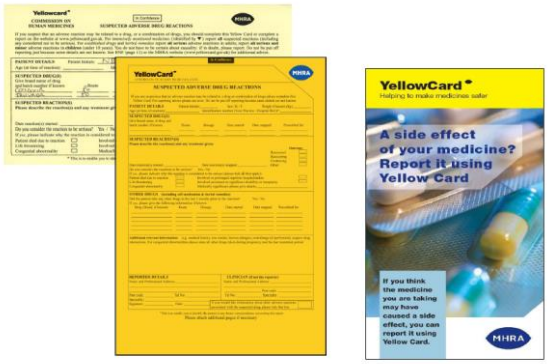
## Pharmacovigilance Reporting Systems (Postmarketing/Safety Surveillance, Spontaneous Reporting Systems)

The core **data-generating system** of pharmacovigilance, relying on healthcare professionals and patients to **identify and report any suspected adverse effects from medicines** to **their local or national pharmacovigilance center or to the manufacturer**.

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/.

## Reporting to MedWatch




## Electronic Reporting


## Benefits of Spontaneous Reporting Systems

- Key in monitoring patient safety
- Particularly useful for new medications where clinical trials:
  - Exposed small numbers of people
  - Short duration
  - Unlikely to detect ADRs particularly those with frequency of <1/1500 or long latency
- Lack of experience in special patient groups such as pediatric population, elderly, pregnancy
- Important for chronic and long term use
- To detect drug-drug interactions, drug-food interactions

## Severe Cutaneous Adverse Reactions (SCAR) in Oncology

| Drug class | Drug | Pharmacology | References | Total (n) | Mortality | SJS | SJS/TEN | TEN |
|---|---|---|---|---|---|---|---|---|
| Alkylating agents | Treosulfan | Alkysufonates | [6] | 1 | 1 | 0 | 0 | 1 |
| | Chlorambucil | Mustard gas derivatives | [7, 8] | 2 | 0 | 0 | 0 | 2 |
| | Mechlorethamine (topical) | Nitrogen mustard | [9] | 1 | 0 | 1 | 0 | 0 |
| | Temozolomide | Hydrazines and triazines | [10] | 1 | 0 | 0 | 1 | 0 |
| | Procarbazine | Hydrazines and triazines | [11–13] | 3 | 0 | 0 | 0 | 3 |
| Plant alkaloids | Paclitaxel | Taxanes | [14] | 1 | 0 | 1 | 0 | 0 |
| | Docetaxel | Taxanes | [15–19] | 5 | 2 | 3 | 0 | 2 |
| | Etoposide | Podophyllotoxins | [20] | 1 | 0 | 1 | 0 | 0 |
| Anthracyclines | Doxorubicin | | [21] | 1 | 1 | 0 | 0 | 1 |
| Antimetabolites | Methotrexate | Folic acid antagonists | [22–26] | 5 | 2 | 2 | 0 | 3 |
| | Cytarabine | Pyrimidine antagonist | [27, 28] | 2 | 2 | 0 | 0 | 2 |
| | Fludarabine | Adenosine deaminase inhibitor | [29] | 1 | 1 | 1 | 0 | 0 |
| | Gemcitabine | Pyrimidine antagonist | [30–32] | 3 | 0 | 2 | 1 | 0 |
| | Capecitabine | Pyrimidine antagonist | [33] | 1 | 0 | 1 | 0 | 0 |
| | Cladribine | Purine antagonist | [34, 35] | 2 | NA | 1 | 0 | 1 |
| | 6-Mercaptopurine | Purine antagonist | [36] | 1 | NA | 0 | 0 | 1 |
| | TS-1 (tegafur-gimeracil-oteracil potassium) | | [37, 38] | 2 | 0 | 1 | 0 | 1 |
| | Pemetrexed | Multitarget antifolate | [39, 40] | 2 | 0 | 0 | 0 | 2 |
| Antitumor antibiotics | Bleomycin | | [41, 42] | 2 | 1 | 0 | 0 | 2 |
| | Pepkomycin | | [43] | 1 | 0 | 1 | 0 | 0 |
| | Mithramycin | | [44, 45] | 2 | 0 | 0 | 0 | 2 |
| Miscellaneous | Lenalidomide | | [46–48] | 14 | 2 | 12 | 1 | 1 |
| | Thalidomide | | [49–53] | 5 | 1 | 1 | 0 | 4 |
| | Asparaginase | | [54] | 1 | 0 | 0 | 0 | 1 |
| | | | Total | 60 | 13 | 28 | 3 | 29 |

NA: not available.

Journal of Immunology Research 2018; 1-9

## Individual Case Safety Reports (ICSR)

- Reports sent by health professionals or patients when an adverse effect has occurred in a patient taking one or more medicines.


- 49-year old female patient
- Diagnosis: Bipolar Disorder
- Treatment: Antipsychotic medication started one year before the reported adverse events
- After stopping therapy, she developed "dizziness, can hardly walk and feet are going numb"
- Concomitant therapy: not provided
- Outcome: unknown

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/, Accessed May 2018

## Four Requirements for a Valid Case Report

- ✓Patient
- ✓Drug product
- ✓Adverse event
- ✓Reporter

FDA, 2018

## Evaluation of Case Reports

- Adverse event occurrence in expected time
- Absence of symptoms prior to exposure
- Positive dechallenge or rechallenge
- Consistent with pharmacologic effects
- Consistent with known effects in the class
- Support from pre-clinical studies, clinical trials
- Absence of alternative explanations

FDA, 2018

## Elements of an Informative Postmarketing Report

- Description of adverse event
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

FDA, 2018

## Exercise

- Read each case reports and classify them as:
  - Valid and non-valid case
  - Informative and non-informative case
  - Related or not related to the medication

## Exercise

| Case | Valid/NV, Informative/NI, Related/NR/Unk |
|---|---|
| Report from a caregiver related to an elderly patient who received unspecified medication and died | |
| Report from a nurse related to a 16 year-old male HIV patient who was on remission but developed disseminated candidiasis that required administration of fluconazole during 3 days and developed generalized rash | |
| Spontaneous report from a cardiologist related to an 85-year old female who was on propranolol for 24 h and developed renal failure | |

## Questions?