

# Pharmacovigilance



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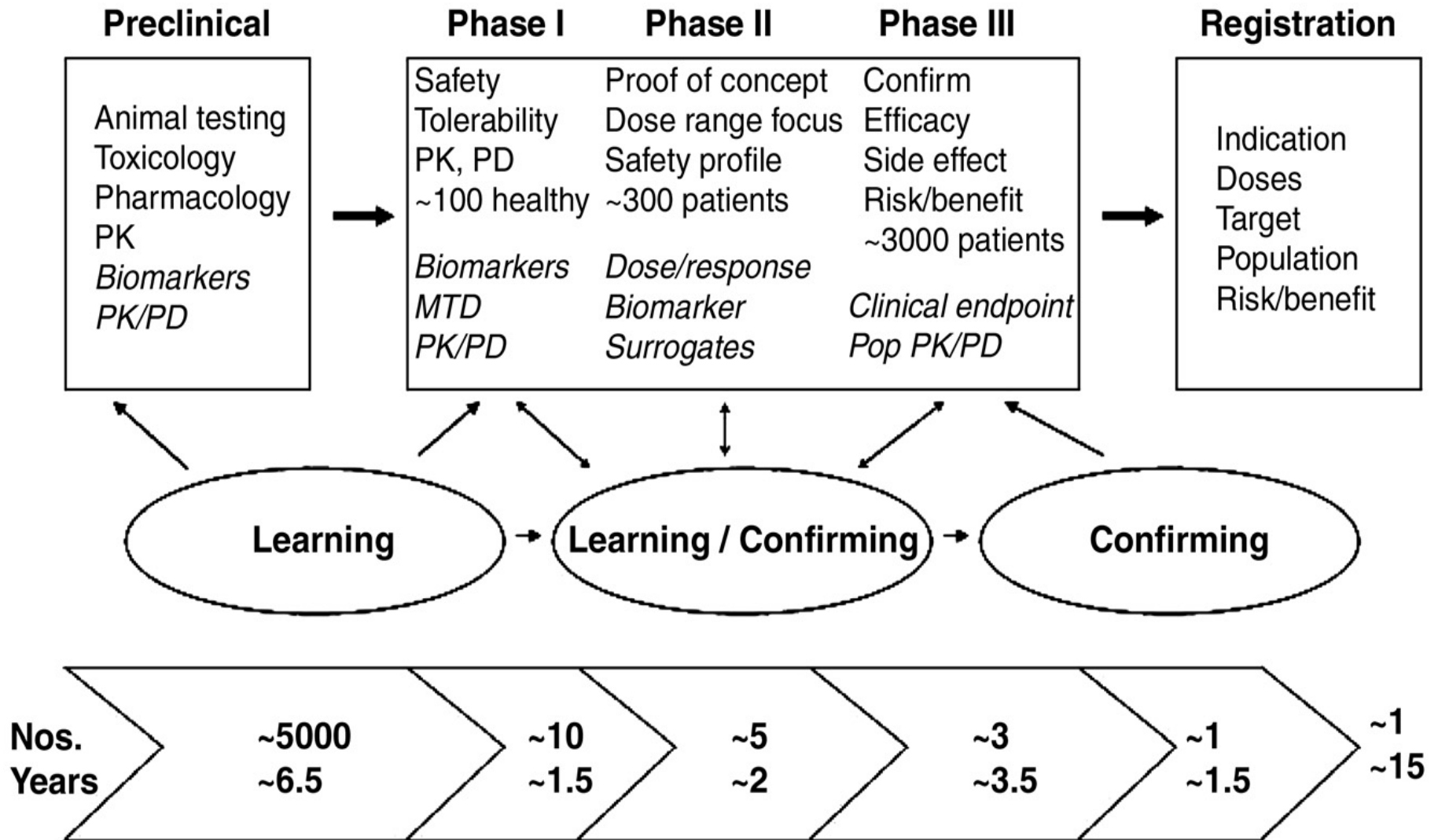
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- World Health Organization defines pharmacovigilance as, “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”.

# Definition

- **Pharmacovigilance** is the post marketing surveillance and study of ADRs
  - With the ultimate goal of preventing or minimizing their occurrence
- Pharmacovigilance is the pharmacological science relating to the detection , assessment ,understanding and prevention of ADRs
- The last phase in drug development

## Clinical Investigations



- The conduct of pharmacovigilance by the industry and health authorities includes:

➤ collection

➤ compilation

➤ quality control and

➤ analysis



of the spontaneous reports

- **Their evaluation must bear on:**
  - the validity of reports,
  - the causal assessment of the cases,
  - the adverse events' severity and outcome,
  - the signaling value (newness) of the cases  
and its impact on the benefit/risk ratio of  
the drug

# Adverse Drug Reactions (ADRs)

- *“any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function” / WHO/*

- Adverse drug event
  - *Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment*
- Side Effect
  - *Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug*



## Events that are not ADRs

- Side effect
- Drug withdrawal symptom,
- drug abuse syndrome,
- accidental poisoning, and
- drug-overdose complications
  - should not be defined as ADR

# ADR?

- drowsiness or dry mouth due to administration of antihistamines.
- nausea associated with the use of anti-neoplastics.

# Program Features

- An ADR-monitoring and reporting program should include the following features:
  - All health professionals should be educated on the importance and benefit of ADR reporting
  - They should be encouraged to report any suspected ADR to the pharmacist

- Simplify process for reporting suspected ADRs by developing an ADR reporting form
- Program should be ongoing
- System should respect the confidentiality of the patient and facility
- ADR reporting should be promoted through an ongoing campaign

# Role of the Pharmacist

- To promote the development, maintenance and ongoing evaluation of a program to reduce the risk of ADRs through *detecting, reporting and assessing* any suspected ADR
  - Investigate every suspected ADR for its nature, probability and severity
  - Develop risk reduction strategies as part of an ongoing program
  - Enlist the continued support of other health professionals in this program

- ***Detection***

- Identify triggers that signal an investigation by the pharmacist.

- Examples: abrupt discontinuation of a drug, multiple patients with similar unwanted symptoms on the same drug therapy, and the use of any drugs to treat a symptom rather than a disease /corticosteroids, epinephrine, antihistamines/

- Provide information to other health care professionals to better identify ADRs.
  - E.g. list common ADRs by therapeutic category

- ***Assessment***

- Review reports of suspected ADRs and differentiate between obvious medication errors and suspected ADRs
- Use a validated algorithm to determine the probability that the event is drug related



- Categorize severity
- Track ADRs for patterns and incidence
- Interact with other professionals as appropriate

- ***Reporting***

- Provide feedback to physicians, nurses, residents and family members about ADRs
- Report ADRs in a systematic way that allows appropriate analysis and intervention
- Disseminate information about previously unreported ADRs

## ***Risk reduction strategies***

- Educate staff and encourage compliance with the ADR reporting program.
  - Include the importance of ADR reporting, identified trends, common signs and detection tips.

- Develop prospective review systems for reducing ADRs.

Example:

- target drug projects,
- residents on high-risk medication (Warfarin, NSAIDs etc),
- residents on greater than 5 medications, and
- routine monitoring of abnormal laboratory values and high risk patients

- Provide in-service programs based on identified trends in reporting and appropriate changes in treatment
- Pharmacists should strive to enhance their knowledge in geriatric and pediatric pharmacotherapy.

# Pharmacovigilance Methods

1. Passive surveillance
2. Intensified reporting
3. Active surveillance
4. Comparative observational studies
5. Targeted clinical investigations
6. Descriptive studies

### 1. Passive surveillance

- Spontaneous reports
- Case series

#### Spontaneous reports

- events/reactions that are **voluntarily** reported either to pharmaceutical manufacturers, to national/regional pharmacovigilance centers, or to national regulatory authorities by health care professionals, other professionals or consumers

- Early warning signals
- Relatively inexpensive
- Do not interfere with clinical practice



## **Limitations of Spontaneous reports**

- Information inadequate, incomplete, not verifiable
- Cause- effect difficult to establish
- Voluntary, thus under reporting
- Incidence and prevalence difficult to calculate

## Case series

- Series of case reports can provide evidence to generate hypothesis as to the relation b/n drug exposure and outcome

## 2. Intensified reporting

- **Stimulated reporting in the early post marketing phase.**
  - Drug manufacturers might actively provide health professionals with safety information and at the same time **encourage** cautious use of new products and the submission of spontaneous reports when adverse event is identified

- A plan can be developed before the product is launched
- This is still a form of spontaneous event reporting
- the data obtained may suffer similar limitations as the passive surveillance system does.

### **3. Active surveillance**

- Seeks to completely ascertain the number of adverse events via a continuous pre-organized process:
  - Sentinel site surveillance
  - Drug event monitoring
  - Registries

## **Sentinel site surveillance:**

- Reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites (hospitals, pharmacies, nursing homes etc.)
- Limitations of sentinel sites are problems of selection bias, small number of patients and increased costs

- Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes etc.
- Institutional settings can have greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting

## Drug event monitoring:

- Patients might be identified from electronic prescription data or automated health insurance claims
- A follow up **questionnaire** can then be sent to each prescribing physician or patient at pre-specified interval to obtain outcome information



- Questionnaire should include information on:
  - patient demographics, indication for treatment, duration of therapy, dosage, clinical events and reasons for discontinuation

- Poor physician and patient response rates and unfocussed nature of data collection, which can obscure important signals, are some of the **limitation** of drug event monitoring

## Registries:

- A list of patients presenting with the same characteristics such as disease (disease registry) or a specific exposure (drug) registry
- Collect information using standardized questionnaires in prospective fashion

- Disease registries, such as registries for blood dyscariasis, severe cutaneous reactions or congenital mal-formations can help collect data on drug exposure

- Exposure/drug registry addresses population exposed to medicinal products of interest to determine if the drug has a special impact on this group of population
- Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires

## 4. Comparative observational studies

- There are a number of observational study designs that are useful in **validating** signals from spontaneous reports/case series
- Major types of design are case-control studies and cohort studies

## 5. Targeted Clinical Investigations

- When significant risks are identified from pre-approval clinical trials, further **clinical studies** might be called for to evaluate the mechanism of action for the adverse reaction.

- Pharmacodynamic and kinetic studies may be conducted to determine whether a particular dosing instruction can put patients at an increased risk of Adverse Events
- Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions.



## 6. Descriptive Studies

- Used to establish the **incidence** and **prevalence** of the outcome of interest including the description of disease treatment patterns and adverse events

# Pharmacovigilance : Methods

## PASSIVE SURVEILLANCE

- Spontaneous ADR reporting
- Case series

## ACTIVE SURVEILLANCE

- Sentinel site surveillance (hospitals, pharmacies, nursing homes etc.)
- Drug event monitoring
- Registries

## COMPARATIVE OBSERVATIONAL STUDIES

- Case control study
- Cohort studies

**Intensified reporting**

**Targeted Clinical Investigations**

- Pharmacodynamic and kinetic studies
- Genetic testing

**Descriptive Studies**

# Case Causality Assessment

- 4 causality criteria:
  - quantitative measures (OR),
  - risk factors
  - temporal characteristics and
  - non-temporal event characteristics

- Quantitative measures (RR, OR)
- Risk factor
  - Will the suspected drug in particular patient produce AE is based on whether the absence and presence of risk factors such as co-medication, or intercurrent illnesses, excessive dosage, previous occurrences of AE without the drug exposure etc...

- Temporal characteristics:
  - Time to onset
  - Course (including dechallenge)
  - Rechallenge

- **Time to onset (delay in appearance) of the event:**
  - Interval between the critical dose (first dose, last dose, incorrect dose, overdose) for the particular patient and first manifestations of the event

- **Type of course in relation to dechallenge**  
**(duration of an adverse event):**
  - the *total duration of the event* normally refers to the period of **the event during treatment** with the suspected drug plus **the period after the dechallenge.**



- The clinical **course after cessation or reduction in dose** may give a clue to a dose dependent effect (if the event is not irreversible)
- The time could be divided into two:
  - The dechallenge dependent and
  - Dechallenge independent segment

## The dechallenge dependent segment

- In the dechallenge dependent segment, **course after dechallenge** is the interval between the last dose of the product and disappearance of the reaction

- Two courses can occur after dechallenge:
  1. The event disappears (+ve dechallenge \_ possible causal link)
    - where we need to note **time to improvement** (interval between last dose and the beginning of the disappearance) or **time to resolution** (interval between the last dose and complete disappearance).

Type of course in relation to dechallenge cont...

2. The event persists/worsens: may be interpreted **against** the event's being related to the drug in question.

The dechallenge independent segment

- Depending on whether the event began before or after the last dose of the drug in question, **two situations are possible:**

- a. The event began before the last dose: either the event lasts as long as the treatment with the suspected drugs or event disappears before stopping the drugs

- b) The event began after the last dose: although it occurred outside the treatment window, a causal relationship to a drug is still possible.
- For single use drugs/injections or vaccines this is always the case
  - the first dose is the same as the last dose.

- ***Re challenge:***
  - refers to whether the event recurred after the reintroduction of the suspect drug
- ***Pre challenge:***
  - during the causality assessment **any previous exposures to the drug**, whether and when they occurred, and whether the AE appeared at that time should be assessed (generally part of the case risk factors)

# Non-temporal Characteristics

- *Pharmacology*
  - *Pathology*
  - *Topography and*
  - *Semiology*
  - ***Pharmacology:***
    - Based on the nature of the ADR.
- E.g. if AE is bradycardia and one of the suspect drug is a beta-blocker, then this is a pharmacologic criterion favoring the beta-blocker as **the causative agent**.



- Based on response to an antagonist/antidote.

E.g. Naloxone is used to treat narcotic (morphine, codeine, etc) overdoses

- **Pathology:**

- Some rare adverse reactions are always due to medications.

- Example, fixed drug eruption (the only cutaneous reaction whose cause is clearly associated with a drug/xenobiotic taken systematically).

## Topography: in-situ reactions

- Reactions seen **at the application site or at a site of high concentration** should be considered as non-temporal factors favoring the causality of the suspect drug.

Examples :

- ✓ injection site pain,
- ✓ transit site esophageal obstruction by **a sticky** drug and
- ✓ nephrolithiasis from a drug metabolite concentrated and crystallized in urine.

## Semiology: altered clinical presentation

- Certain diseases manifest themselves differently when they are due to drugs than when they occur on their own

- Example, drug induced lupus erythematosus differs from idiopathic lupus erythematosus as it presents incomplete clinical picture such as fever, malaise, and polyarthralgia whereas pleuritis and pericarditis are less likely and renal complications are very rare

# Data assessment in Pharmacovigilance

1. Individual case report assessment
2. Aggregated study and interpretation:
  - Signal detection
  - Risk factors, interactions
  - Serial (clinicopathological) study
  - Frequency estimation

# Individual case report assessment

## Components of a case report

- Patient
- Adverse event
- Drug exposure (suspected and other)
- Source

# Patient

- Age
- Sex
- Medical history
- Case identification (confidential)



# Adverse event

- Description: aspect, place, severity, diagnosis
- Outcome, course, time relationship ('challenge, dechallenge, rechallenge')
- Laboratory data

# Suspected drug

- Name (product, generic, ingredients, batch no.)
- Dose, route, dates (interval, duration)
- Indication

# Aggregated study and interpretation

## 1. Signal detection

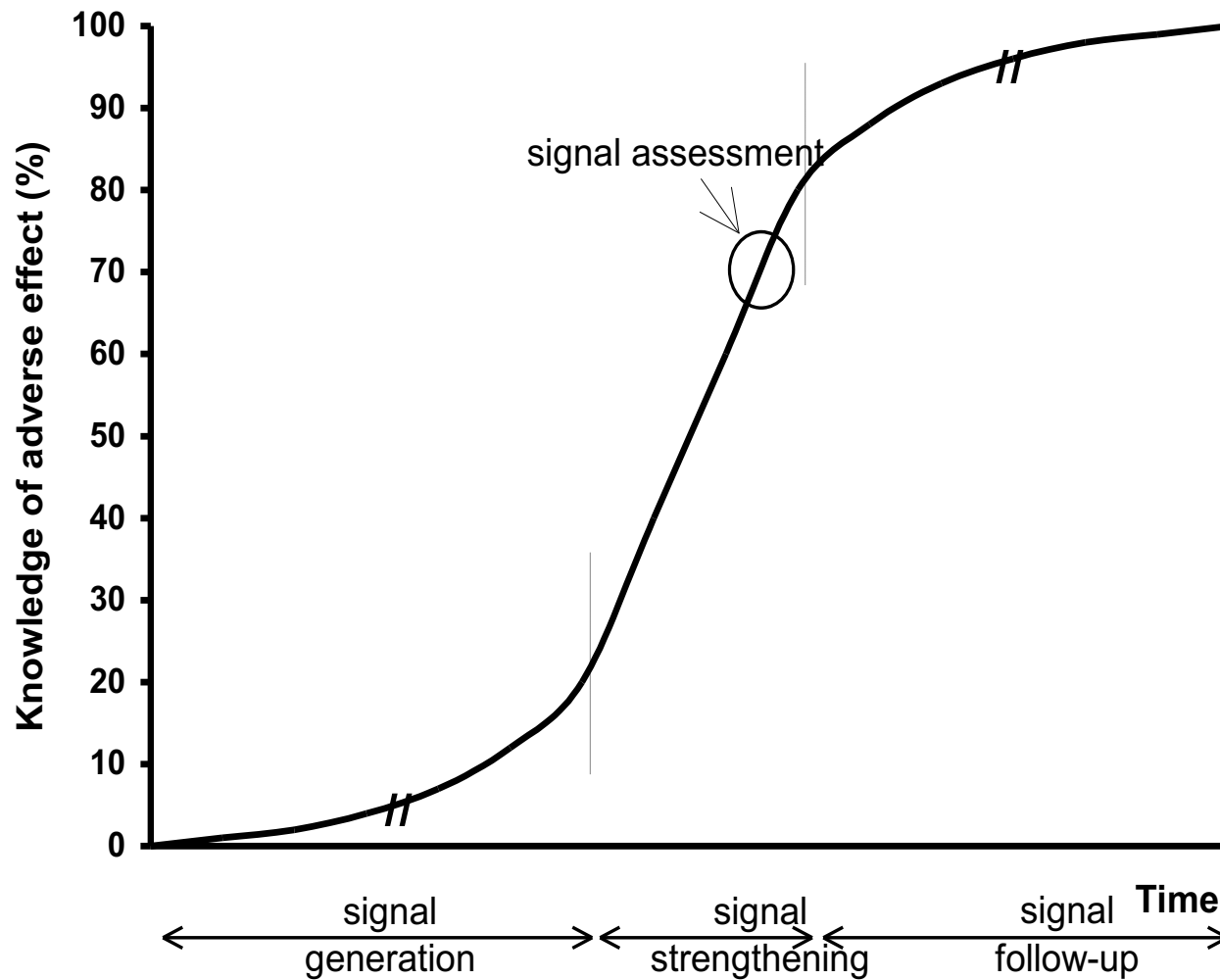
a signal is reported information on a possible causal relationship between an adverse event and a drug, the relationship being **unknown or incompletely documented previously / WHO-UMC /**.

- Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

*Edwards IR, Biriell C. Drug Safety 1994; 10:93-102*

# Data of a signal

- Qualitative (clinical)
- Quantitative (epidemiological)
- Experimental



## Signal Detection

- Selection of a possibly relevant association  
(hypothesis generation)
- Preliminary assessment of the available evidence  
(signal strengthening)

## 2. Signal follow-up

# Criteria for selecting a signal

+

- Unknown adverse reaction
- Unexpected
- Strong statistical connection
- Low background frequency
- Specific, characteristic
- Objective (definitive) event
- Typically drug-related event or  
Critical Term
- Serious
- High potential relevance

-

- Known (and labelled)
- Expected but 'unlabelled'
- Weak statistical connection
- High background frequency
- Unspecific, trivial event
- Subjective event
- Common disorder, e.g. infectious  
or 'endogenous'
- Not serious
- Low relevance



# When is a signal likely to be relevant?

- *Early Warning*
  - New adverse reaction; new drug
- *Public health perspective*
  - Important drug (serious indication; widely used)
  - Serious reaction
  - Large number of cases; rapid increase in reporting
  - Regulatory intervention (prevention)

# Acceptability of An Adverse Drug Reaction

- It is a value judgment
- ADR is deemed acceptable when its frequency and severity are sufficiently compensated for by the frequency and magnitude of the therapeutic benefit of the drug

- Examples: severe GI bleeding with a mild analgesic; headache seen with AIDS or cancer medication would be deemed acceptable.
- Acceptability can be seen at two levels:
  - In Clinical Practice and
  - On a population level

**In Clinical practice:** a clinician makes decision whether or not to modify the treatment in a given patient:

- ***Before the occurrence of an ADR:*** in a newly diagnosed hypertension, the physician may hesitate between prescribing a thiazide diuretic and a beta-blocker. However, the presence of asthmas in the patient makes the beta-blocker unacceptable

– ***After the occurrence of an ADR:*** a hypertensive patient has an acute episode of gout after having started treatment with thiazide, which makes this treatment unacceptable- substitute with beta-blockers.

– ***After the occurrence of an ADR but before the occurrence of the desired beneficial effect:*** a

patient suffering from prostatitis has been taking antibiotics. There is no improvement in his symptoms and complaining of abdominal discomfort associated with the medication - the ADR is deemed unacceptable -treatment discontinuation

- ***After the occurrence of an ADR and after the occurrence of desired beneficial effect:*** a hypertensive patient tolerates neither thiazides nor beta-blockers.

The patient BP is well controlled with an angiotensin converting enzyme inhibitor but with mild dry cough.

- mild cough may be acceptable since a good pharmacologic control of BP has been obtained.

## **On population level:**

- Before market authorization
- After market authorization



# Actions Taken

- Transmission of information: label changes
  - A reduction in a recommended dose
  - A removal of one or more indications
  - Use of the drug as a secondary/tertiary treatment rather than a primary treatment

- Recommendation of concomitant treatment with another drug to prevent or correct the problem produced by the drug
- Recommendations of periodic lab testing or clinical follow up

- An absolute/relative restriction on the population being treated
- A new contraindication for patients with certain medical conditions (concomitant morbidity)

- Limitation of access to the drug
  - Alteration of availability: narcotic, controlled drug, limited prescription, temporary use authorization
  - Limitation on the prescribers e.g. reserved only to specialists

- Limitation on methods of prescription (limitation of number of tablets dispensed, no telephone prescription, no automatic renewal etc
- Obligatory laboratory testing e.g. negative pregnancy test result before, during and possibly for some months after stopping of treatment

- Modification of the product itself
  - **Change in the active ingredient:** removal/  
substitution of one of the active ingredients in a  
combination product
  - **Change in the Galenic form:** change and removal of  
excipients, modification of the quantity in the bottle  
or box, change in packaging, change in accompanying  
device

- **Change in storage/preparation:**

E.g. For a refrigerated injectable product that produced pain and burning on injection-marked improvement resulted after the label was **changed** to indicate that it should be at room temperature before injection

- Withdrawal from market
  - Withdrawal of a particular active ingredient, a specific product, a specific formulation
  - Temporary or definitive suspension of sales
  - Cessation of manufacture and distribution
  - Withdrawal of stocks from the wholesaler, pharmacist or patient depending upon the severity



THANK you