Pharmacovigilance

What is Pharmacovigilance ?

- Data gathering related to the detection, assessment, understanding, and prevention of adverse events
- Identifying new information about hazards associated with medicines, preventing harm to patients
- Post-marketing surveillance (?)
- Medical errors are broader category which includes adverse reactions but also other factors (diagnostic errors, equipment failure, nosocomial infections ...)

Withdrawn Drugs (in the US, since 2000)

Drug	Year	Reason
Lumiracoxib	2008	Hepatotoxicity
Aprotinin	2008	Kidney and cardiovascular toxicity
Tegaserod	2007	Cardiovascular ischemic events
Ximelagatran	2006	Hepatotoxicity
Valdecoxib	2005	Dermatology adverse events
Pemoline	2005	Hepatotoxicity
Rofecoxib	2004	Thrombotic cardiovascular events
Levomethadyl	2003	Fatal Arrhytmia
Rapacuronium	2001	Risk of fatal bronchospasm
Cerivastatin	2001	Rhabdomyolosis
Trovafloxacin	2001	Hepatotoxicity
Amineptine	2000	Hepatotoxicity, dermatological side effects, abuse potential
Cisapride	2000	Cardiac arrhythmias
Troglitazone	2000	Hepatotoxicity

- Other drugs were restricted in use to exclude some patient populations or indications - Alosetron
- Some drugs were withdrawned and reintroduced after further studies or special safety measures – Natalizumab withdrawn in 2005 and reintroduced in 2006

Do you know ?

- Number of deaths resulting from medical errors in the US may be 100 000 per year.
- Medical errors are among leading causes of death (4^{th} - 6^{th}) – more prevalent then motor vehicle accidents. 5 % of all deaths may be caused by pharmaceuticals.
- Medical errors lead to excess costs ($ 37 B/year in the US), health injury
- Medical errors are preventable in large scale (at least in 50 %) but in some cases new approaches are needed

It should be recognized

- Each drug has its side effects
- Pharmacological/toxic effect frontier is only defined by dose quantity and may differ from patient to patient. Theoretically each drug can be toxic.
- There are efficient mechanisms how to tackle both expected and unexpected adverse drug reactions. Medicines safety is principal task of regulatory agencies.

Terms

- Adverse Event (AE) – any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a casual relationship with this treatment
- Adverse Drug Reaction (ADR) – a response to a drug which is noxious and unintended, and which occurs at doses normally used in man.
- Serious Adverse Event (SAE) – AE that is either life-threatening, fatal, cause of prolong hospital admission, cause persistent disability or concern misuse or dependence

Terms

- Serious Adverse Drug Reaction (SADR) – ADR where SAE conditions of severity applies
- Unexpected Adverse Drug Reaction (UADR) – an adverse reaction, the nature or severity of which is not consistent with market authorization, or expected from the characteristics of the drug.

Expected and Unexpected Events

- Expected are those adverse events that were observed during clinical trials or post-approval observations and are mentioned in Summary of Product Characteristics (SPC)
- Unexpected are those adverse events that were not previously observed and are not documented (in SPC)
- Based on frequency of occurrence there are following categories of adverse events:

Category	Frequency
Very common	≥ 1/10
Common	≥1/100 and <1/10
Uncommon	≥ 1/1,000 and <1/100
Rare	≥ 1/10,000 and <1/1,000
Very rare	< 1/10,000

Avandia (Rosiglitazone) Adverse Reactions - SPC

Table 1. The frequency of adverse reactions identified from clinical trial data

Adverse reaction	Frequency of adverse reaction by treatment regimen			
	RSG	RSG + MET	RSG + SU	RSG +MET +SU
Blood and the lymphatic system disorders				
anaemia	Common	Common	Common	Common
leucopaenia			Common	
thrombocytopaenia			Common	
granulocytopaenia				Common
Metabolism and nutrition disorders				
hypercholesterolaemia[1]	Common	Common	Common	Common
hypertriglyceridaemia	Common		Common	
hyperlipaemia	Common	Common	Common	Common
weight increase	Common	Common	Common	Common
increased appetite	Common		Uncommon	
hypoglycaemia		Common	Very common	Very common
Nervous system disorders				
dizziness*		Common	Common	
headache*				Common
Cardiac disorders				
cardiac failure[2]			Common	Common
cardiac ischaemia[3*]	Common	Common	Common	Common
Gastrointestinal disorders				
constipation	Common	Common	Common	Common
Musculoskeletal and connective tissue disorders				
bone fractures	Common			
myalgia*				Common
General disorders and administration site conditions				
oedema	Common	Common	Very common	Very common

RSG - Rosiglitazone monotherapy; RSG + MET - Rosiglitazone with metformin; RSG + SU - Rosiglitazone with sulphonylurea; RSG + MET + SU - Rosiglitazone with metformin and sulphonylurea

Types of Adverse Reactions (Rawlins and Thompson Classification)

Type A Effects (“Augmented”)

- Due to pharmacological effects
- Are dose related – may often be avoided by using doses which are appropriate to the individual patient
- Are common, can be experimentally reproduced, known before marketing
- Example: hypnotic effect after H2 antihistaminics

Types of Adverse Reactions (Rawlins and Thompson Classification)

Type B Effects (“Bizzard”, idiosyncratic reactions)

- Generally rare and unpredictable
- Little or no dose relationship, not related to drug pharmacodynamics
- Occur in predisposed, intolerant patients – can be explained by rare genetic polymorphism, allergic reactions
- Example: Penicilline allergies

Types of Adverse Reactions (Rawlins and Thompson Classification)

Type C Effects (“Continuous”)

- Adverse reactions after long term therapy
- There is often no suggestive time relationship and the connection may be very difficult to prove. The use of a drug increases the frequency of “spontaneous” disease
- Example: carcinogenesis

Types of Adverse Reactions (Rawlins and Thompson Classification)

Type D Effects (“Delayed”)

- Adverse effect may be presented years after a drug was used
- Example: Vagina cancer of daughters when their mother was treated by diethylstilbestrol

Type E Effects (“Ending”)

- Absence of drug after withdrawal – rebound effect
- Example: corticosteroids in asthma treatment

Causality Assessment

To determine likelihood of a causal relationship between drug exposure and adverse events it is necessary to evaluate

- Association in time/place between drug use and event
- Pharmacology (including current knowledge of nature and frequency of adverse reactions)
- Medical or pharmacological plausibility (signs and symptoms, tests, pathological findings, mechanism)
- Likelihood or exclusion of other causes

Causality Assessment

- There are more assessment scales for causality evaluation which include:
  - Karch and Lasagna scale
  - Naranjo scale
  - WHO probability scale
  - Jones scale

Karch and Lasagna

- Uses three categories of causality
  - A – causality is highly probable
  - B – not adequate proof of causality
  - 0 – data are not adequate to assess causality

Causality Assessment

NARANJO's ALGORITHM

question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	-1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when drug was readministered?	+2	-1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Classification of Adverse Events based on its severity

- Mild – no changes in therapy are needed
- Moderate – change of therapy is desired but the events are not life-threatening or causing disability
- Serious – is either life-threatening, fatal, cause of prolong hospital admission, cause persistent disability

Pharmacology in Adverse Reactions

- Detailed safety profile of a drug can only be evaluated and described on base of clinical research and postmarketing surveillance
- However, there are some factors that can be associated with higher safety risks. These risk can be on side of:
  - Administered drug
  - Patient
  - Environment (xenobiotics, physical conditions)
- Higher safety risks are associated with medicines with no specific mechanism of action such as neuroleptics (haloperidol, chlorpromazine), non-selective cyclooxygenase inhibitors, cytostatics, morphine analgetics
- Another group is medicines with narrow therapeutic range (i.e. low therapeutic index) – cardiac glycosides, aminoglycoside antibiotics (gentamycin), theophylline
- Therapeutic index = Median Toxic Dose (TD50)/ Median Effective Dose (ED50)

Risks dependent on Patient

- Kidney insufficiency – failing excretion of drugs/active metabolites
- Liver disease – failing drug metabolism
- Polymorbidity – combination of factors such as drug interactions, multi-organ injury
- Immunocompetence – higher doses of some drugs (antibiotics) may be needed in decreased immune response
- New born age – drug metabolizing systems are not fully developed
- Allergies – risk of drug allergies is higher in patients with already suffer from another allergy
- Some specific diseases – such as contraindication of beta blockers in asthma

Pharmacogenetics

- Study of how individual`s genetic inheritance affects response to drugs
- Genetic polymorphisms in metabolizing enzymes can cause substantial differences in drug response. Some polymorphisms are very rare
- Genetic testing was developed to detect various polymorphisms in metabolizing enzymes (CYP 450) – this opens possibility of personalized prescribing to avoid adverse events

Important enzymes in drug metabolism with more known polymorphisms

- Cytochrome P450 polymorphisms – influence metabolism of various drugs
- Thiopurine Methyltransferase (TMT) – metabolism of thiopurines
- Acetyltransferases

Another mechanism is interaction with Human Leukocyte Antigen system (HLA) - klozapin, levamizol, carbamazepine

Risks dependent on Other Factors

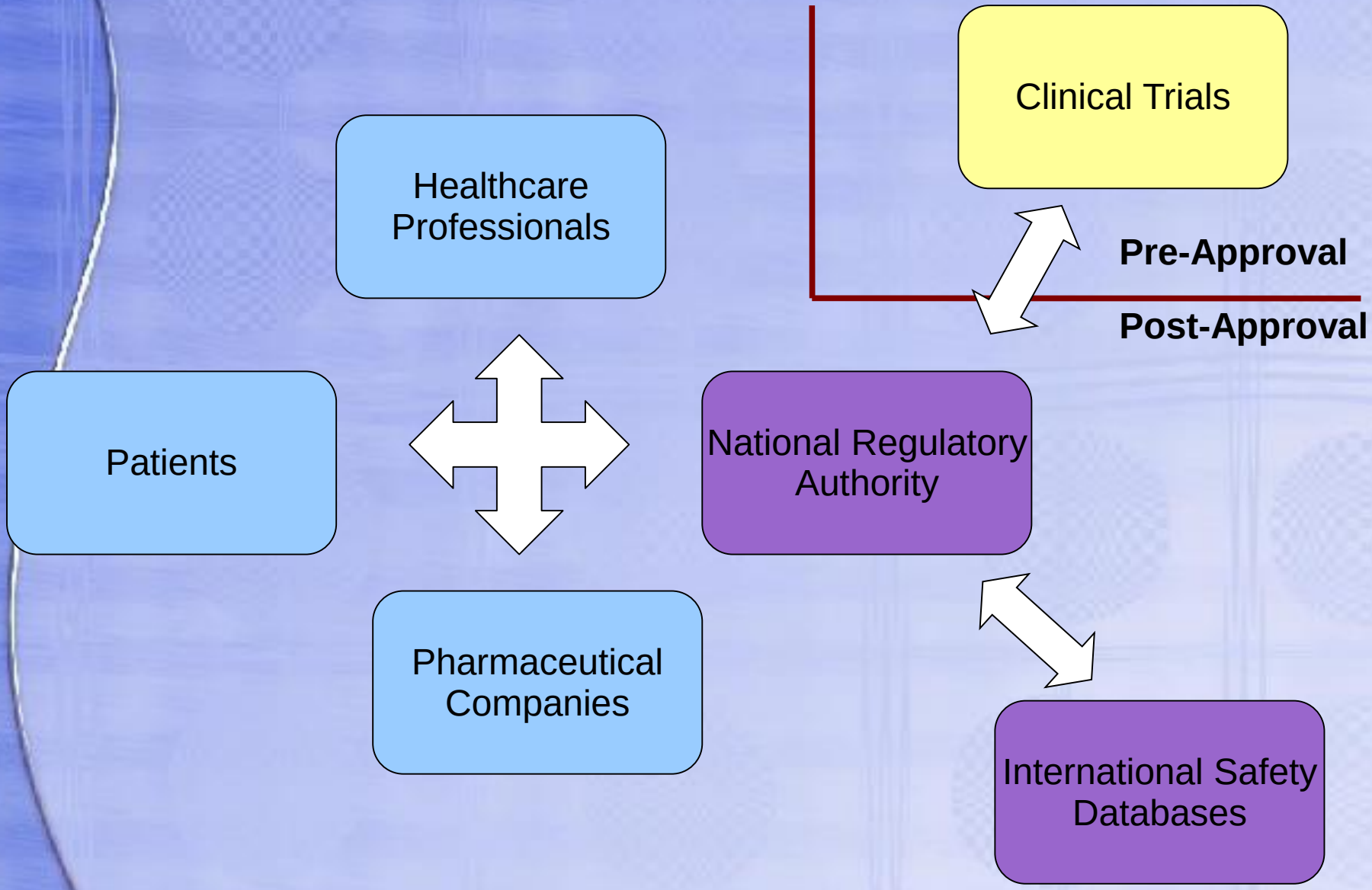
Drug dependent

- Drug interactions

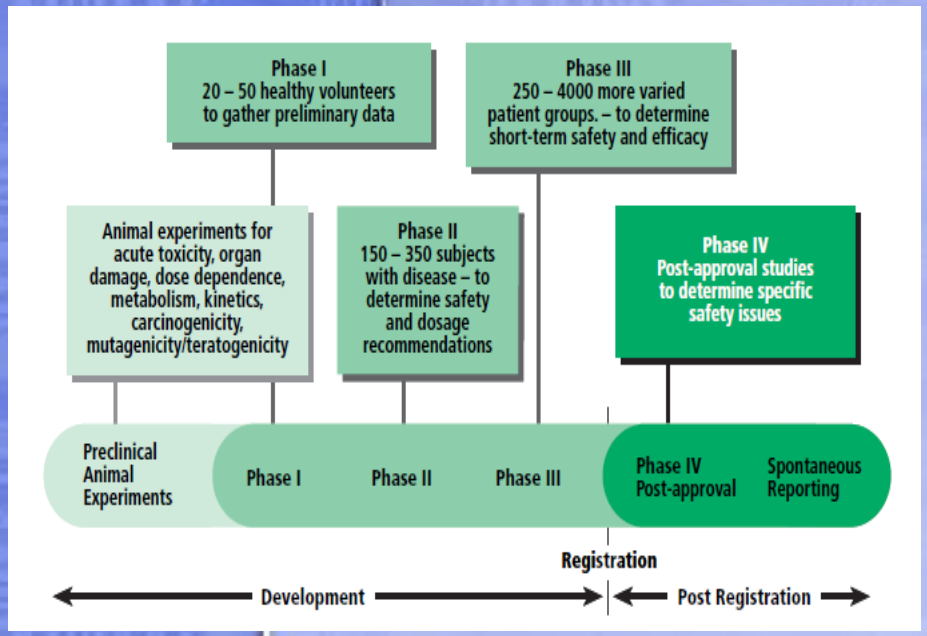
Environment dependent

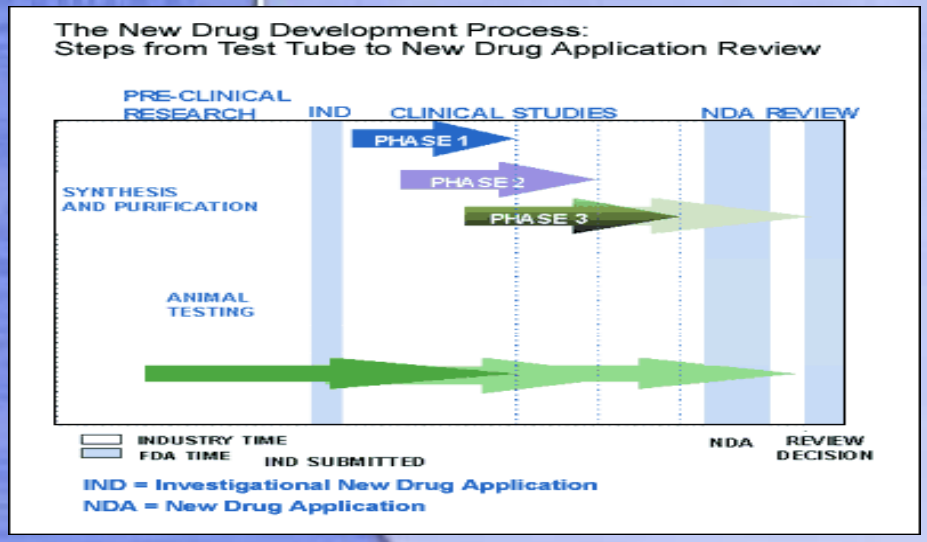
- Xenobiotics (pesticides, veterinary antibiotics) can interact with drugs metabolism, most commonly on CYP 450 level

System of Safety Data Gathering



New Drug Approval Process





- Each new drug (New Chemical Entity, NCE) shall prove its safety and efficacy in order to gain marketing authorization
- Scientific data on efficacy/safety are collected in clinical trials
- If a drug meets all safety (and efficacy) requirements New Drug Application (NDA) is submitted to regulatory agency
- Regulatory agency reviews the application, may require further studies. It issues Marketing Authorization (MA) or reject application, guided by risk/benefit evaluation
- Research of drug safety continues after drug is introduced in clinical praxis as post-marketing surveillance (phase IV study)

Cerivastatin Case Study

- Cerivastatin was developed by Bayer to compete with other statins. Rhabdomyolysis cases were rare in other statins (3.3 per 100 000 patient-years).
- Cerivastatin gained US marketing authorization in June 1997 as cholesterol lowering agent and cardiovascular disease prevention. It was introduced to US market in early 1998 under brand names Baycol and Lipobay.
- Soon after (until May 1998) Bayer received 6 SADRs of cerivastatin associated rhabdomyolysis in patients also taking gemfibrozil. This was followed by label update – rhabdomyolysis warning.
- First case of rhabdomyolysis associated with cerivastatin-gemfibrozil combination published in April 1999.
- July 1999 - Clinical trial of 1.6 mg cerivastatin reveals high incidence of severe CK elevation (12 %) but the results are not published.
- Gemfibrozil-cerivastatin coprescription is contraindicated in December 1999

Cerivastatin Case Study

- By 2000, 549 cases of rhabdomyolysis associated with cerivastatin use has been reported to WHO Collaborating Centre in Uppsala
- Higher risk compared to other statins was admitted by Bayer in March 2000
- Label update of April 2001 stated 0.4 mg as starting dose (it became clear that higher doses are associated with higher elevated CK levels)
- That time Bayer performed study on the risk of myopathy. This study was later criticized because of its poor design but results has not been published. The final report was provided to the company in June 2001.
- Bayer voluntarily withdraws cerivastatin worldwide on August 8th 2001
- FDA publish research in 2002 which found mortality rates from rhabdomyolysis for cerivastatin users were 16 to 86 times higher than those of other statins. However, rhabdomyolysis asscociated with cerivastatin was found to be 270 cases per 100 000 patient-years (most cases were not fatal) in patients taking 0.4 mg cerivastatin.
- Bayer faced approx. 8000 lawsuits in connection to Baycol/Lipobay

International Cooperation in Drug Safety

- EudraVigilence – data processing network for reporting and evaluating suspected adverse reactions of medicinal products in European Economic Area
- WHO Monitoring Centre in Uppsala
  - Established in 1978
  - Coordination of the WHO programme for International Drug Monitoring
  - Collection, processing of data, Education, Research

Sources of Information on Drug Safety

- Pre-clinical studies
- Clinical trials (pre- and post-marketing)
- Spontaneous adverse reaction reporting
- Epidemiological studies
- Data collected for other purposes
  - Routine statistics
  - Databases of prescription and outcomes

Pre-clinical Studies

Standard toxicology pre-clinical tests are:

- Acute toxicity
- Repeat use toxicity
- Local irritation tests
- Pyrogenity
- Reproductive toxicity
- Mutagenity
- Carcinogenity

Clinical Trials

- Principal aim of clinical is to collect safety (and efficacy) data. The investigational drug shall prove safety profile consistent with human testing on base of pre-clinical studies. Clinical trials are subject of regulatory approval.
- The sponsor shall keep detailed records of all adverse events and he shall submit these records on request of regulatory authority.
- The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions have to be recorded and reported to regulatory authority
- Other investigators participating in multicentric trials shall also be informed on serious unexpected adverse events

Clinical Trials

- Safety profile of investigational drug is described in Investigator`s Brochure (likewise SPC in marketed drugs
- Procedures for reporting of adverse events in clinical trials slightly differ from post-approval reporting. Standard are CIOMS forms, electronic reporting is now preferred
- Detailed guidance on the collection, verification and presentation of adverse reactions reports arising from clinical trials on medicinal products for human use, European Commission, April 2006
- Serious events such as deaths are relatively rare and may present reason for termination of a clinical trial

Rationale for Post-Marketing Surveillance

- Tests in animals are insufficiency predictive of human safety
- In clinical trials patients are selected and limited in number
- Conditions of use in trials differ from those in clinical practice
- Duration of trials is limited
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups such as children, the elderly or pregnant woman or drug interactions is often not available

Who Should Report Safety Data

- Physicians
- Pharmacists
- Pharmaceutical companies qualified persons – (Pharmacovigilence/Regulatory manager)
  - Investigational products (clinical trials)
  - Post-approval reporting – Individual Case Safety Report (ICSR), Periodic Safety Update Report (PSUR)
- In many countries patients are encouraged (but not obligated) to report side effects

What to Report – WHO recommendations

- Every single problem related to the use of a drug, because probably nobody else is collecting such information
- All suspected adverse reactions
- ADRs associated with radiology contrast media, vaccines, diagnostics, drugs used in traditional medicine, herbal remedies, cosmetics, medical devices and equipment
- Lack of efficacy and suspected pharmaceutical defects
- Counterfeit pharmaceuticals
- Development of resistance

What to Report (at least)

- Requirements for reporting differ from country to country. However, in each developed country healthcare professionals are legally obligated to report adverse reactions (although it is not always clearly stated which)
- It is important to report serious unexpected ADRs – those that are not described in SPC. Unexpected include also side effects mentioned in SPC when these occur in higher frequencies then described.
- Most cases of unexpected ADRs are associated with medicines newly introduced on the market
- It has no sense to report expected ADRs
- In clinical praxis it is usually not easy to evaluate causality – report also in cases you are not sure about causal relationship
- Heathcare professionals may report adverse events also to marketing authorization holder for a medicine but are not obligated to

Potential Sources of Errors in Pharmaceutical Care

- Handwriting of prescriptions
- Prescribing doctors missing information on other prescriptions for a patient (drug interactions)
- Similar-sounding and look-alike names and packages of medication
- Level of stress on workplace
- Unclear records in information system
- Bad system of stock alignment/organization
- Disruptions in information availability and flow

Solutions

- It is expected that 50 – 75 % of medical errors are preventable
- Introduction of advanced medical information systems
  - Electronic Health Record (EHR)
  - Automatic checks for dose, interactions, allergies, resistance
  - Personalized prescription (on base of pharmacogenetic data)
- Written procedures, quality management and safety audits
- Analyze all errors, research what enabled them
- Try to design uncomplicated processes