What kind of risk is acceptable for drugs ?

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For medicinal products, the acceptability of serious adverse events depends on the seriousness of the disease and on the patient group treated.

For blood, is this acceptability patron the same ?

Adverse reaction rates of medicinal products

Definitions:

- Common: > 1/100 to < 1/10 patients.
- Uncommon: > 1/1,000 to < 1/100 patients.
- Rare: > 1/10,000 to < 1/1,000 patients.
- Very rare: < 1:10,000 patients, including individual cases

Is an adverse reaction equivalent to risk ?


AZ

Safety in health care is a priority

Moral obligation	Common sense	We do it for ourselves
• **Healthcare company obligated to protect safety of medicines used by patients** • **Regulatory basis** • **Legal basis**	• **Healthcare professionals and patients must trust that medicines are safe** • **Safety is good business**	• **We are healthcare professionals** • **We are patients** • **Our families and children are patients**

“To err is human: building a safer health system”

US: annually, 4,000 – 7,000 patients die due to medication failures

Recommendations:

- **Increase knowledge on safety of risk processes by mandatory national reporting system in order to learn from failures made.**
- **Target setting on patient safety in a health care organization**
- **Implementation of safety management systems to create safety culture and monitoring system on the level of individual patient**

Institute of Medicine, 2000

Serious adverse drug reactions

Serious adverse drug reactions cause or contribute to:

- 6-7 % of all hospitalizations
- A 2-day increase in the average length of hospitalization
- 100,000 death in the US
- May cost about as much a drug treatment itself

Eichelbaum et al. Annu Rev Med 2006;57:119-37

Reported adverse drug reactions

Period 1998-2005:

- Numbers of reported ADRs and deaths related to such ADRs increased both by a factor of about 2.6.
- 4 % of all new medical agents are withdrawn due to ADRs

Period 1995-2005:

- > 34 drugs withdrawn mainly due to hepatotoxic or cardiotoxic effects

Eichelbaum et al. Annu Rev Med 2006;57:119-37.
Moore et al. Arch Intern Med 2007;167:1752-9.
Need at al. Nat Genet 2005;37:671-81.

Failures in hospitals in The Netherlands

- **Annually, 1,735 patients die because on unintended damage**
  - Of these, 150 die because of medication failures (8.6%)
- **Of all failures in hospitals, 30% is related to medicines.**
- **Annual expected number of reports: 15,000**
- **30 % due to administration failures**
  - 30% of administration failures: wrong doses
  - 30% of administration failures: not-prescribed medicine or wrong medicine
  - 25% of administration failures: not giving indicated medicine

EMGO/Nivel study 2007

Failures in hospitals in The Netherlands

Failures:

- administration of 1 liter of glucose 50% instead of glucose 5%.
- 10 ampoules of MgCl interpretation failure: mmol and mg.
- Methotrexaat: daily during eight days instead of once a week.

Problems:

- read-alikes (only the first and the last letter is being red, dobutamin and dopamin)
- sound-alikes.

EMGO/Nivel study 2007

Safety of drugs

- Increasing insight that at the moment of registration of medicinal product, not everything is known on the safety profile
- Increasing interest of public, media and politicians in the risks of medicinal products
- Pharmacivigilance develops more and more scientifically

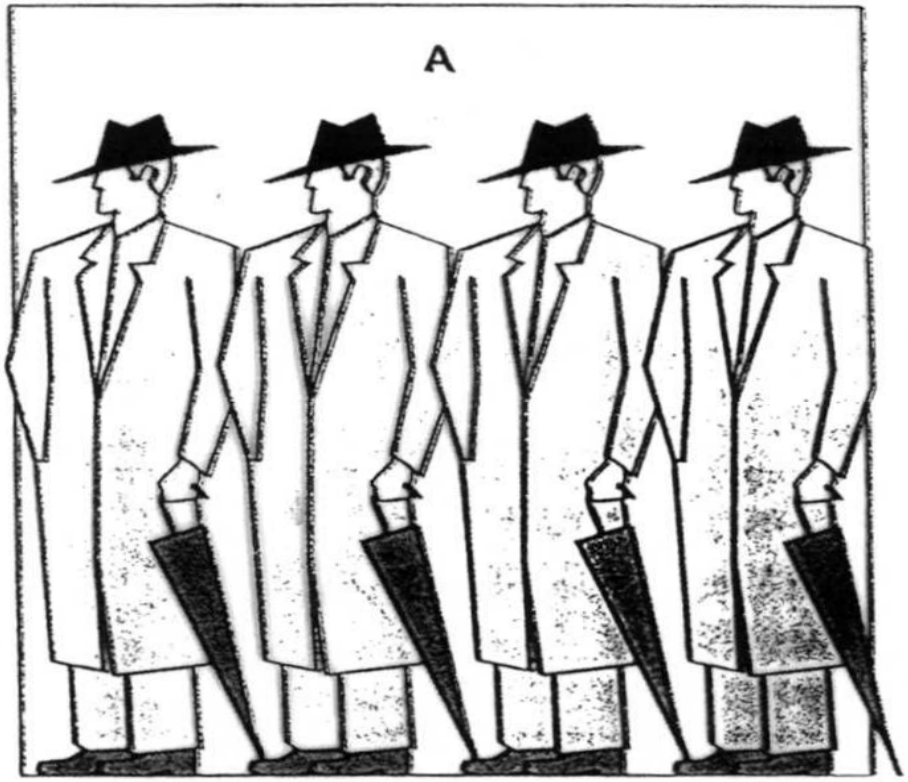
Re-registering

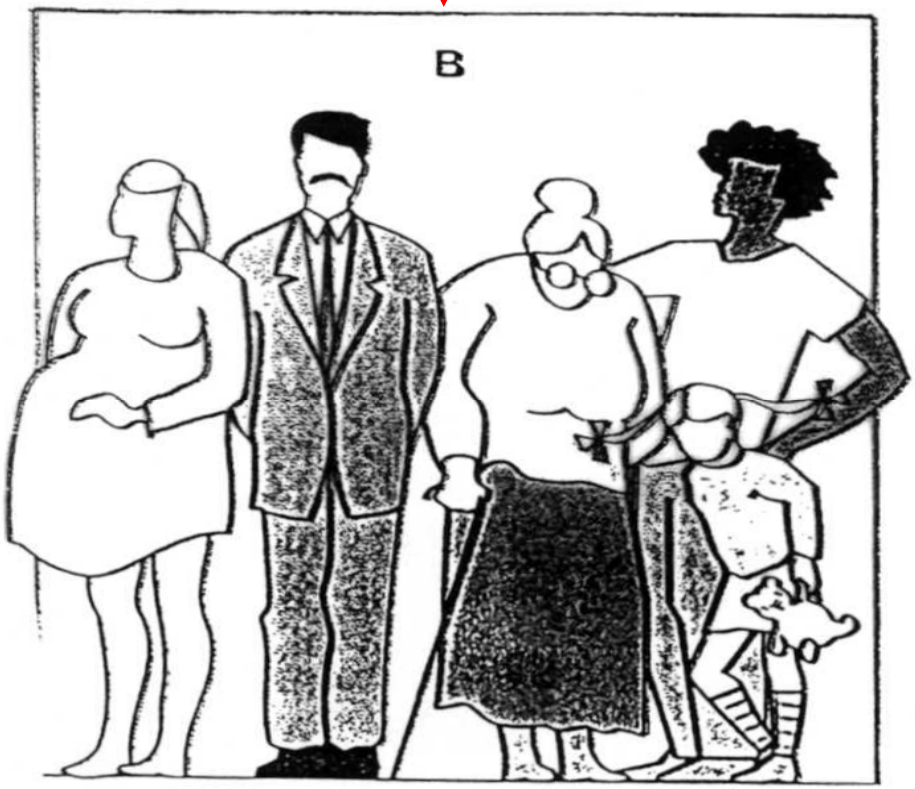
Safety profile not complete due to limited number of (kind of) subjects participating in trials:

- Rare adverse events are missed
- Patients with co-morbidity excluded from trials
- Patients of certain age categories excluded from trials

Pre-registration study population

Actual users population

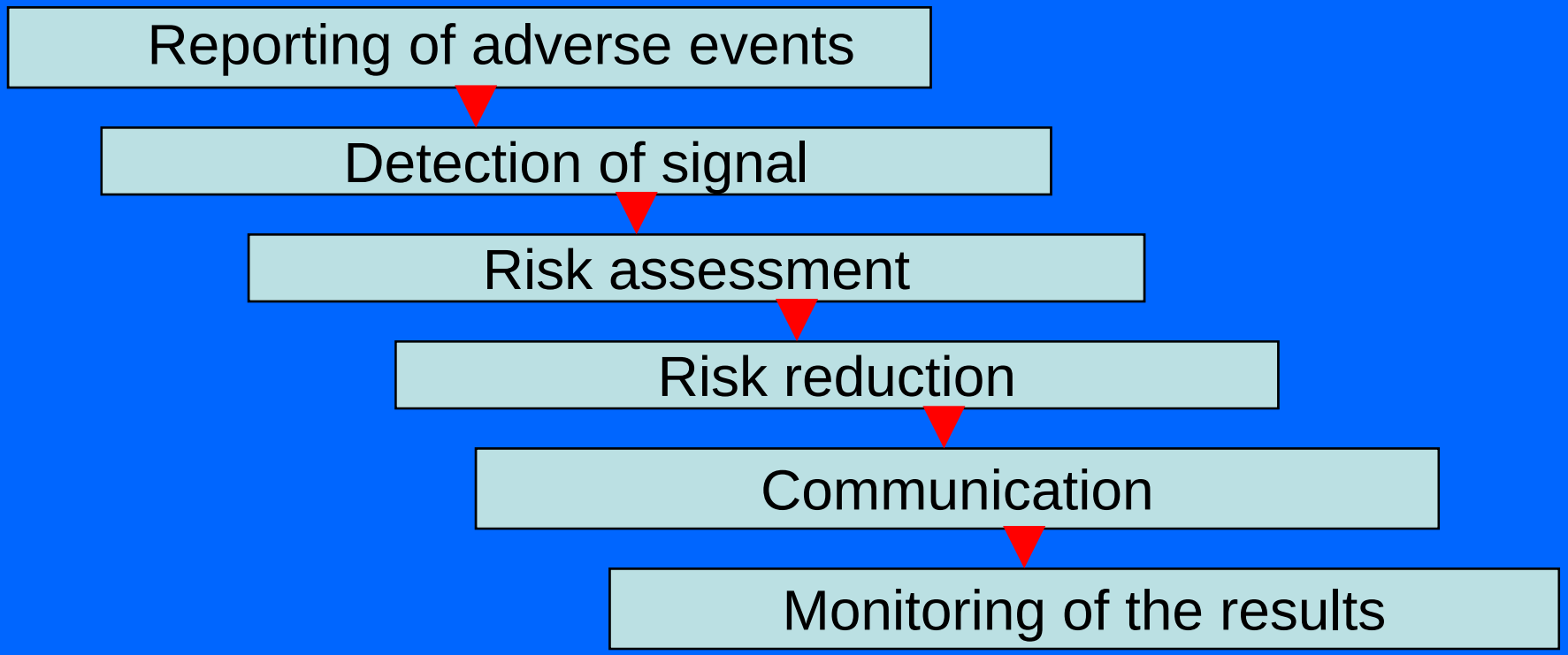




What to gain ?

- System of spontaneous reporting not enough
- More input from pharmaco-epidemiology
- Pro-active approach: introduction of risk management

Pharmacovigilance chain



Reporting and risk detection

- Eudravigilance data bank on adverse events
- National data banks on adverse events and WHO data bank
- Introduction of ‘intensive monitoring’ after market introduction
- Periodic safety update reports
- Results from risk management plans

Risk assessment

- Confirmation of the signal
  - Pharmaco-epidemiology
  - Clarifying mechanism
- Determination of risk factors and risk patients
- Use of results of Risk Management Plan
- Her-evaluation of the risk / benefit balance

Risk reduction

- Recall of product from the market
- Adjustments of SPC and inserts
- Implementation of special risk reducing measures from the risk management plan

Communication on the risks and taken measures

- ‘Dear Doctor’ letter
- Press releases
- Publications in scientific literature
- Patient organizations
- Part of risk management plan

EU Risk Management Plan

Defined for registration of new medicines or at observation of safety problem of existing product

- **Part I (= ICH E2E)**
  - Safety specification (what do we know and what do we don't ?)
  - Pharmacovigilance plan (how are the holes filled?)

- **Part II**
  - Evaluation of the need for special risk reducing measures, and if so:
  - Description of these specific risk reducing measures

WORLD HEALTH ORGANIZATION
ORGANIZATION MONDIALE DE LA SANTE

Patients Safety Solutions

Any system design or intervention
that demonstrated the ability
to prevent or mitigate patient harm stemming
from processes of health care

May 2007

WHO Collaborating Center for Patient Safety Solutions

WHO Patient Safety Solutions

Nine inaugural patient safety solutions:

- Look-alike and sound-alike names
- Patient identification
- Communication during patient hand-overs
- Performance of correct procedure at correct body site
- Control of concentrated electrolyte solutions
- Assuring medication accuracy at transitions in care
- Avoiding catheter and tubing mis-connections
- Single use of injection devices
- Improved hand hygiene to prevent health care-associated infections

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Scientific approaches to the safety of medicinal products

Attempts to predict adverse events ?

Is it possible to prevent adverse events ?

Scientific approaches to the safety of medicinal products

Attempts to predict adverse events ?

- Naranjo-score

Is it possible to prevent adverse events ?

ADR probability scale

	yes	no	do not know	score
Are there previous *conclusive* reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction re-appear when placebo was given?	-1	+1	0	
Was the reaction detected in the blood (or other fluids) in concentration known to be toxic?	+1	0	0	
Was the reaction more severe when the does 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 any objective evidence?	+1	0	0	
Total score				

Naranjo et al. Clin.Pharm.Ther.1981;30,2;239-245

ADR probability scale

- Useful for structural judgementing of different aspects of suspected adverse events
- In almost all cases, conclusion ends with ‘possible’ causality
- ‘Possible’ causality is in Naranjo-system low ranked level of causality

  (doubtful-possible-probable-definite)

- Conclusion: sensitivity low

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Scientific approaches to the safety of medicinal products

Attempts to predict adverse events ?

Is it possible to prevent adverse events ?

- Dose adjustment based on organ dysfunction
- Interventions of potential interacting medication

Scientific approaches to the safety of medicinal products

Attempts to predict adverse events ?

Is it possible to prevent adverse events ?

- Dose adjustment based on organ dysfunction
- Interventions of potential interacting medication
- Pharmacogenetics

Is it possible to prevent adverse events ?

Search for pharmacogenomic biomarkers

Patients at increased risk due to genes encoding for:

- drug-metabolizing enzymes
- altered enzymatic activity leading to elevated levels of substrate drug
- increased of amounts of reactive metabolites
- risks on immune–mediated toxic effects (MHC class I genes)

Ingelman-Sundberg. New Engl J Med 2008;358;6:637-9

Abacavir

- guanosine reverse-transcriptase inhibitor -

- 1 mill. HIV + patients
- 5 – 8 % patients: serious hypersensitivity reaction (fever, rash, gastrointestinal tract symptoms, other organs)
- 2002: highly associated with HLA-B*5701 gene
- Studies in Australia, UK, France (2002-2005): no ADR in HLA-B*5701 negative patients
- ADR due to cytokines release involving HLA-B*5701 and a proposed endogenous peptide
- Resume: High selectivity of HLA-B*5701 as a pharmacogenomic biomarker

Ingelman-Sundberg. New Engl J Med 2008;358;6:637-9

Pharmacogenomic biomarkers for prediction of severe adverse drug reactions

Pharmacogenomic biomarkers as predictors of adverse drug reactions			
Gene or allele	Relevant drug	Specificity of biomarker	Percent of patients with an adverse reaction to drug
TPMT (mutant)	6-Mercaptopurines	very good	1-10
UGT1A1*28	Irinitecan	good	30-40
CYP2C9 and VKORC1	Warfarin	good	5-40
CYP2D6 (mutant)	Tricyclic antidepressants	relatively good	5-7
HLA-B*5701	Abacavir	very good	5-8
HLA-B*1502	Carbamazepine	very good	10
HLA-DRB1*07 and DQA1*02	Ximelagatran	good	5-7

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Pharmacogenomic biomarkers for prediction of severe adverse drug reactions

- Only seven useful examples, including TPMT-or CYP2D6-polymorfisme in case of azathioprine (6-Mercaptopurines) or tricyclic antidepressants, respectively.
- Examples for effective pharmacogenomic test with high sensitivity and modest specificity to avert specific toxic effects of drugs.

Ingelman-Sundberg. New Engl J Med 2008;358;6:637-9

In summary

- Pro-active approach has started
- Legislation changes have been implemented
- EU, US and WHO cooperation more and more intensified
- Pharmacoviglance becoming adult

But: usage of medicinal products will never be without risks