Signal Detection And Risk Management

Module 9 Topic 5

WHO definition of a 'signal'

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to detect a potential signal, depending upon the seriousness of the event and the quality of the information"

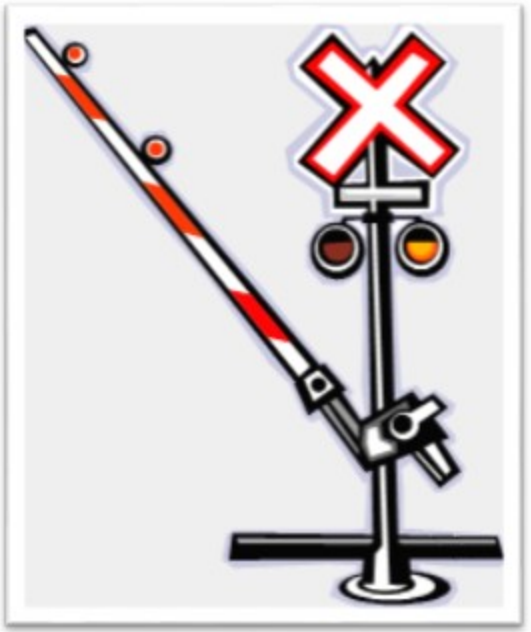
defined by the World Health Organisation (Meyboom et al 1997)

CIOMS VI definition of a 'signal'

"A report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance"

Council for International Organizations of Medical Sciences

(CIOMS VI, 2005)



Signal Sources

- Clinical Studies- company sponsored & others, pre and post marketing
- Single cases, case series in aggregate review, PSURs
- Literature, internet, newspapers
- WHO database
- Post marketing from prescribers, consumers, other regulatory bodies, ECs, IRBs

Sources of Signals (1)

- Overall, the safety Physician (supported by PS Scientist/Specialist) is accountable for identifying signals
- Clinical Studies
  - Internal study
  - External study
- Review of received adverse event reports (clinical study and spontaneous) in the companie's global safety database
  - Single case(s) - Medical review during the case handling process (selected cases only)
  - Case series - Periodic review of aggregated data & PSURs
  - End of study analysis
  - Safety Management Team meetings

Sources of Signals (2)

- The Literature
- Other media
  - The internet
  - Newspapers
- Quantitative methods
  - External databases
  - Sapphire database

Sources of Signals (3)

- Pharmacoepidemiology
  - Internal study
  - External study
- Pre-clinical studies
  - Internal study
  - External study
- External questions
  - Regulatory bodies
  - Ethics committee
  - Independent Review Board
  - Prescribers
  - Consumers

Is drug x associated with hazard y?

- For signals that require evaluation:
  - Explore data from other sources e.g. preclinical, epidemiology, literature
  - Are new analyses or sub-group analyses of existing data required
  - Be aware of the limitations of the data

Detection

- Large databases collected by companies themselves, regulators or WHO are available
- Data mining and disproportionality analysis are a way to systematically screen spontaneous reports for interesting associations
- Goal is to detect “higher than expected” drug-event frequencies without exposure data
- Latest techniques like Empirical Bayesian Neural network,Proportional Reporting Ratio(PRR) and MGPS (Multi-Item Gamma Poison Shrinker), using exclusive software, have been developed

Factors favoring signal detection (1)

- The clinical event
  - a very low natural frequency
  - characteristic or unusual signs and symptoms
  - occurring in groups of similar patients
  - known to be frequently drug-induced
- Drug exposure
  - high frequency

Factors favouring signal detection (2)

- Adverse Reaction
  - high frequency
  - suggestive time relationship
  - suggestive dose relationship
  - plausible pharmacological and pathological mechanism

Speed of signal detection

- **Depends on:**
  - number of users of the drug
  - frequency of adverse reaction
  - reporting rate
  - quality of documentation

Qualitative vs Quantitative signals

- **Qualitative**
  - small number of cases
  - suggestive time relationship
  - plausible mechanism
- **Quantitative**
  - relative risk calculations
  - more patients - better precision
  - comparisons within drug or between drugs

Criteria for Signal Assessment

- **Quantitative**
  - strength of association
    - number of case reports
    - statistical disproportionality

Methodology of quantitative detection

- Information Component
  - Bayesian statistics
- Odds Ratio
- Proportional ADR Reporting Ratio
- Yule's Q
- Poisson
- Chi square

Disproportionality of reporting

	Event (R)	All Other Events	TOTAL
Medicinal Product (P)	A	B	A+B
All other medicinal Products	C	D	C+D
TOTAL	A+C	B+D	N=A+B+C+D

Criteria for Signal assessment

- Qualitative
  - consistency of data
    - characteristic feature, pattern, absence of reverse findings
  - exposure - response relationship
    - site, timing, dose - response relationship, reversibility
  - biological plausibility
    - pharmacological and pathological mechanisms

Criteria for Signal Assessment (contd)

- experimental findings
  - rechallenge, antibodies, drug concentrations, abnormal metabolites
- analogy
  - previous experience with drug, often drug-induced
- nature and quality of data
  - objectivity of event, validity of documentation, causality assessment

Signal validation

- ask reporter for more details if missing
- ask for opinion from physician/specialist
- causality assessment

Signal strengthening

- Seek information from
  - medical literature
  - other data bases e.g. WHO
  - the manufacturer
  - clinical trial records (if available)
- Analogy with other related drugs

- *Absence of supporting data does not imply false signal*

Seriousness

- Health consequences
  - for individual
  - for public at large
- Determining factor for priority setting and speed of investigation

Mechanism

- Biological plausibility
  - consult textbooks in pharmacology and medicine
  - consult registration dossier
- Pharmacological or ideosyncratic
- Metabolite, degradation product, excipient, impurity

Risk Groups

- Interacting drugs
- Sex
- Age groups
- Dosage
- Duration of treatment
- Route of administration
- Indication

Frequency determination

- Estimate population at risk
  - data from manufacturer
  - sample statistics e.g. IMS
  - health insurance systems
  - drug dispensing outlets
  - drug importation agencies
  - prescription reimbursement systems
  - specific drug utilization studie
- **Determine best and worst case scenario**

Effectiveness/Risk Evaluation

- Risk of
  - no therapy at all (underlying disease)
    - alternative non-drug treatments
    - alternative drug treatments
  - has the benefit/risk situation of drug concerned changed?

Effectiveness/risk Assessment

- Aspects of risk
  - seriousness and severity of reaction
    - duration of adverse reaction
    - frequency of occurrence
- Aspects of benefit
  - seriousness of disease - likely improvement.
  - chronicity of disease - reduction in duration
  - frequency of disease - frequency of improvement

Signal Evaluation

- Signal is prioritised based frequency, seriousness, impact on/risk for patient, company reputation, liabilities and litigations
- Further evaluation could include
  - Sub group analysis of existing data
  - Advanced data-mining
  - Pharmacoepidemiology
  - Plan a new safety study
  - Monitor the signal in all ongoing studies
  - Preclinical study in an animal model
  - Pharmacogenetics / Safety biomarker research

Points to consider

- How strong/robust is the signal?
- What is the importance? (seriousness, health impact)
- Potential business impact
  - Legal exposure
  - Reputation
- Prioritisation of signals
- Phase of Development
- What are the characteristics of the population(s) at risk?

Points to consider

- How to protect patients at current/future risk?
- What is the natural history of the disease being treated?
- Is there an alternative explanation?
- Mechanism/Pharmacological plausibility?
- Pre-clinical data
- Quantitative signal score
- Class effect or event commonly attributed to drugs?

Possible outcomes following evaluation

- No action
- Increased monitoring
- Change product information
  - Addition of new event
  - Modification of current wording
  - Addition of a frequency descriptor
- Restrict use
- Withdraw from the market/stop development
- Inform all stakeholders of the change – ECs, IRBs, doctors, regulatory authorities, licencee partners, consumers

Is technology ultimate?

"The astute clinician reviewing individual cases or case series will remain the mainstay of safety surveillance".

PhRMA

Is technology ultimate?

Many of the known serious ADRs have been recognized by astute clinicians with a high level of awareness, and such awareness is likely to be just as important, as new methods of pharmacovigilance are developed as it has been in the past.

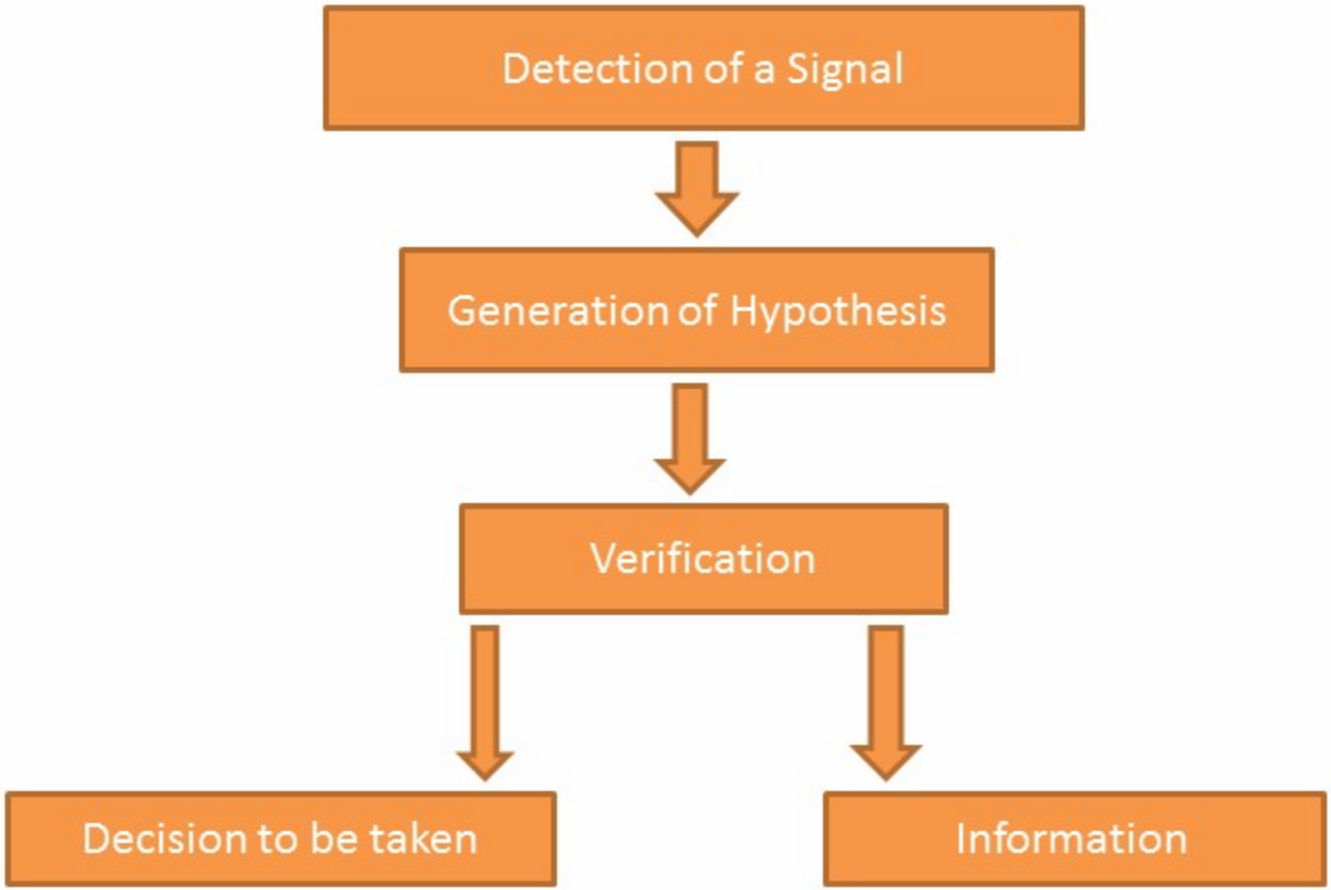
Pharmacovigilance,2nd ed, Editors D. Mann, Elizabeth B Andrews, Wiley 2007

Is technology ultimate? (contd)

A combination of automatic signaling devices and scanning by experienced medical personnel is considered most advantageous to fulfill successfully, the aim of early identification of new ADRs.

Second Edition, Editors D. Mann, Elizabeth B Andrews, Wiley 2007

Signal Detection Process Flow



What is Risk Management?

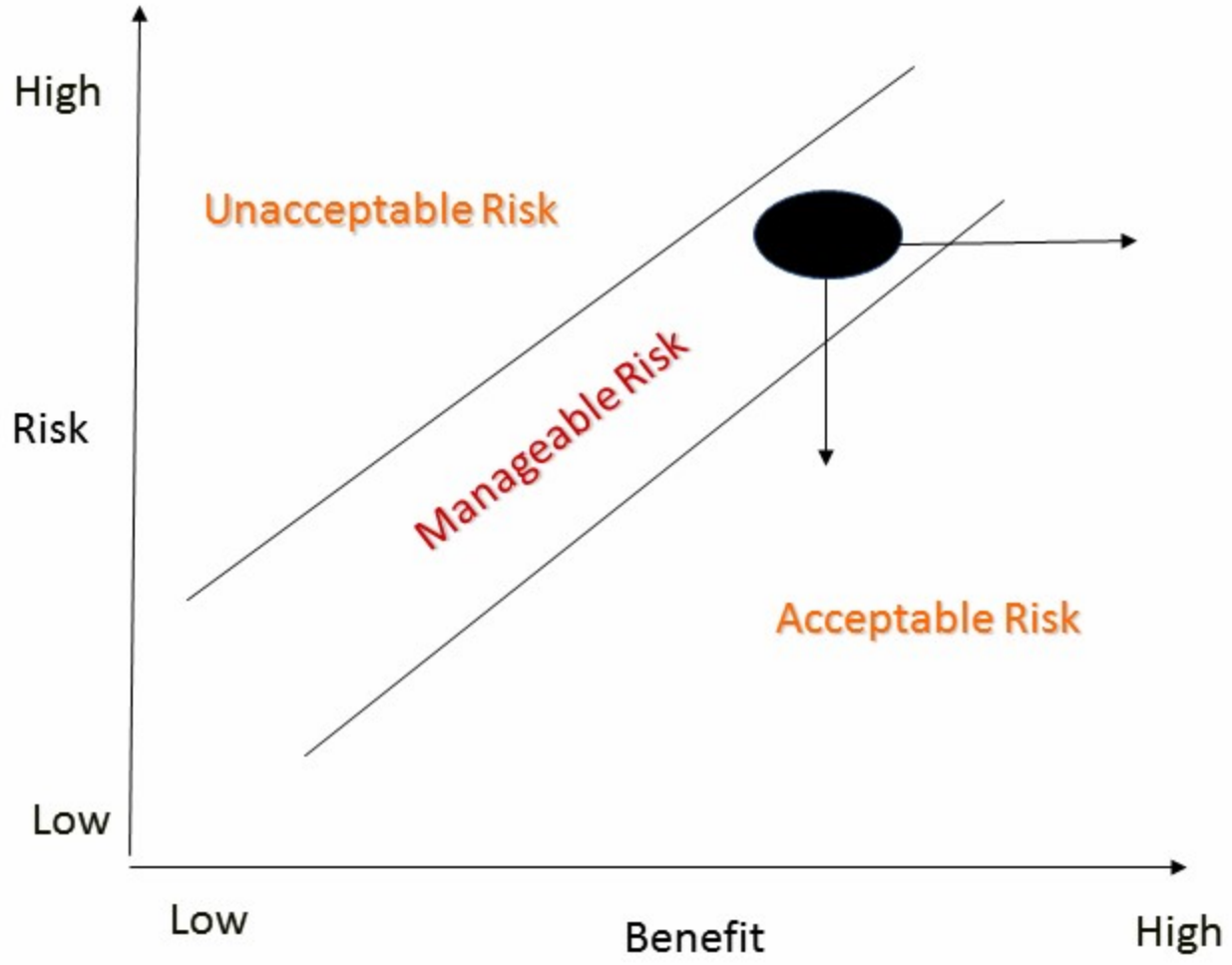
- The activities and interventions deployed to a drug, in order to manage and mitigate known and possible risks, with the aim of protecting the individual
- Identification and implementation of strategies to reduce risk to individuals & populations
- A continuous process of minimising a product's risks throughout its life cycle in order to optimise that product's risk/benefit balance

Why Manage Risk Proactively?

- Regulatory Expectation
  - US, Europe, ICH E2E
- Company Perspective
  - to understand the risk profile
  - to protect the company's asset
- Patient perception
  - expect safe and effective drugs
  - do not fully understand risks
- Need to change prescribing behaviour: labelling not always sufficient

Overall Objectives of Risk Management Planning Benefit - Risk Optimization

Optimizing Benefit Risk



Risk Management Definition

Risk Management

=

Risk Assessment

+

Risk Minimization

Risk Management Strategy

- Product Risk Management Plan

Plan identifying the risks associated with a medicinal product, methods to further clarify the safety profile and ways to minimise risk to individual patients in clinical use

- Three elements

Pharmacovigilance specification

Pharmacovigilance Plan

Risk Minimisation “toolkit”

Basic Components of a Risk Management Plan

Pharmacovigilance Specification

- A structured method of documenting the established risks of a drug and the potential for unidentified risks at the time of marketing authorisation

Risk Management Plan

Purpose

- Assessing risks by focused evaluation to close gaps in knowledge systematically (PM commitments - continued development - targeted populations)
  - looking for potential risks (class effects)
  - following observed events
  - characterizing outcomes that are mulifactorial
- Advance planning and communication of evaluation for new products

Risk Management Plan (contd)

Method

- Integration of incremental data acquisition starting in development, systemizing postmarketing commitments and new indication projects for the newly released compound
- Continued integration of all available data requires start at phase 1