Signal detection and risk management

Module 9 Topic 6

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)

“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 queries from prescribers, consumers, other regulatory bodies, ECs, IRBs

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 favouring signal detection

- 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
- 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

Criteria for Signal Assessment

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

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

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

Signal Detection Process Flow