From Signal Identification to Decision Making
Adverse Reaction 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 one report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

*WHO definition*
Factors favouring 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 V 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
Measures of disproportionality

- Information Component
  - Bayesian statistics
- Odds Ratio
- Proportional ADR Reporting Ratio
- Yule’s Q
- Poisson
- Chi square
Disproportionality of reporting

Reports w the suspected ADR

A

Reports without the suspected ADR

B

Reports w the suspected drug

C

All other reports

D

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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 (continued)

– 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
Risk Groups

• interacting drugs
• sex
• age groups
• dosage
• duration of treatment
• route of administration
• indication
Mechanism

- biological plausibility
  - consult textbooks in pharmacology and medicine
  - consult registration dossier
- pharmacological or ideosyncratic
- metabolite, degradation product, excipient, impurity
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
Benefit/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?
Risk/Benefit 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
Making Decisions

- do nothing, wait for more information
- inform health professionals
- initiate further studies
  - animal studies
  - clinical trials
  - case-control
  - cohort
- alter product information
Making Decisions (continued)

• change marketing conditions
  – limit indications
  – limit availability (specialists, prescription, pharmacy)
  – suspend marketing authorization
  – permanently withdraw marketing authorization

• Consider likely degree of risk reduction
Information

• health professionals first
• press release
• other authorities and WHO
Follow-up

- if no action is taken
  - new reports coming in?
- if action taken
  - effects of action satisfactory?
Steps from Signal to Policy

- early signal identification
- case validation
- signal strengthening
- seriousness
- mechanism
- risk groups
- frequency determination

- risk/benefit evaluation
- decision
- information
- follow-up