Module 8: Signals in drug safety

Introduction

- **WHO Definition of Signal Detection –** Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously
- According to WHO, signal is defined as:
  - Previously unrecognized safety issue
  - Change in severity
  - Change in frequency
  - Identification of at risk group
- **Council for International Organizations of Medical Sciences (CIOMS) VIII Definition of Signal Detection –**

Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be sufficient likelihood to justify verificatory action.

Introduction (2)

- **The United States (US) Food and Drug Administration (FDA) Definition GVPV Guidance –**
- Signals can arise from post marketing data and other sources, such as pre-clinical data and events associated with other products in the same pharmacological class.
- Its possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive challenge or if the event is extremely rare in the absence of drug use.
- Signals generally indicate the need for further investigation which may or may not lead to the conclusion that the product caused the event.

Objectives of Signal Detection

- The first and foremost objective of signal detection is to protect patient's safety.
- The other objective is to meet the regulatory requirements.
- All the relevant data sources should be included e.g. The clinical trials, individual case safety reports (ICSR), periodic safety update reports (PSUR), registries, external databases (FDA, WHO).
- The risk-benefit ratio of the product must be understood.
- The last objective of signal detection is that it must lead to communication of the signal to the patients, MAH, Regulators

Signal Management - Process

1) Signal detection

- ✓The most appropriate methodology for signal detection should be identified depending on the type of product.
- ✓ **Qualitative Signal Detection** is undertaken to detect possible safety signals attributable to an orphan drug
- ✓**2) Signal validation**
- ✓evaluate clinical relevance of the signal (e.g. seriousness/severity, outcome, novelty of reaction, drug interactions, etc.);
- ✓evaluate previous awareness of the signal (e.g. already present in SPC/leaflet, periodic reports, questions from ethics committees, etc.);
- ✓investigate signal using larger sources of information available (e.g. literature, large databases available, etc.).

Signal Management - Process(cont'd)

3) **Signal analysis and prioritisation**

- ✓ Validated signals require urgent attention and need to be prioritised for further management without delay.
- ✓ Prioritization is performed by the **SNIP Method** [**Strength** (e.g. number of cases), **Novelty** (labelled/unlabelled), **Importance** (e.g. severity and seriousness) and **Preventability** (can be prevented or not)]. The SNIP criteria facilitate the consistent and effective evaluation of drug safety signals, producing a standard approach that allows rapid decisions to be made as to whether potential signals are worthy of further attention.

4) Signal assessment

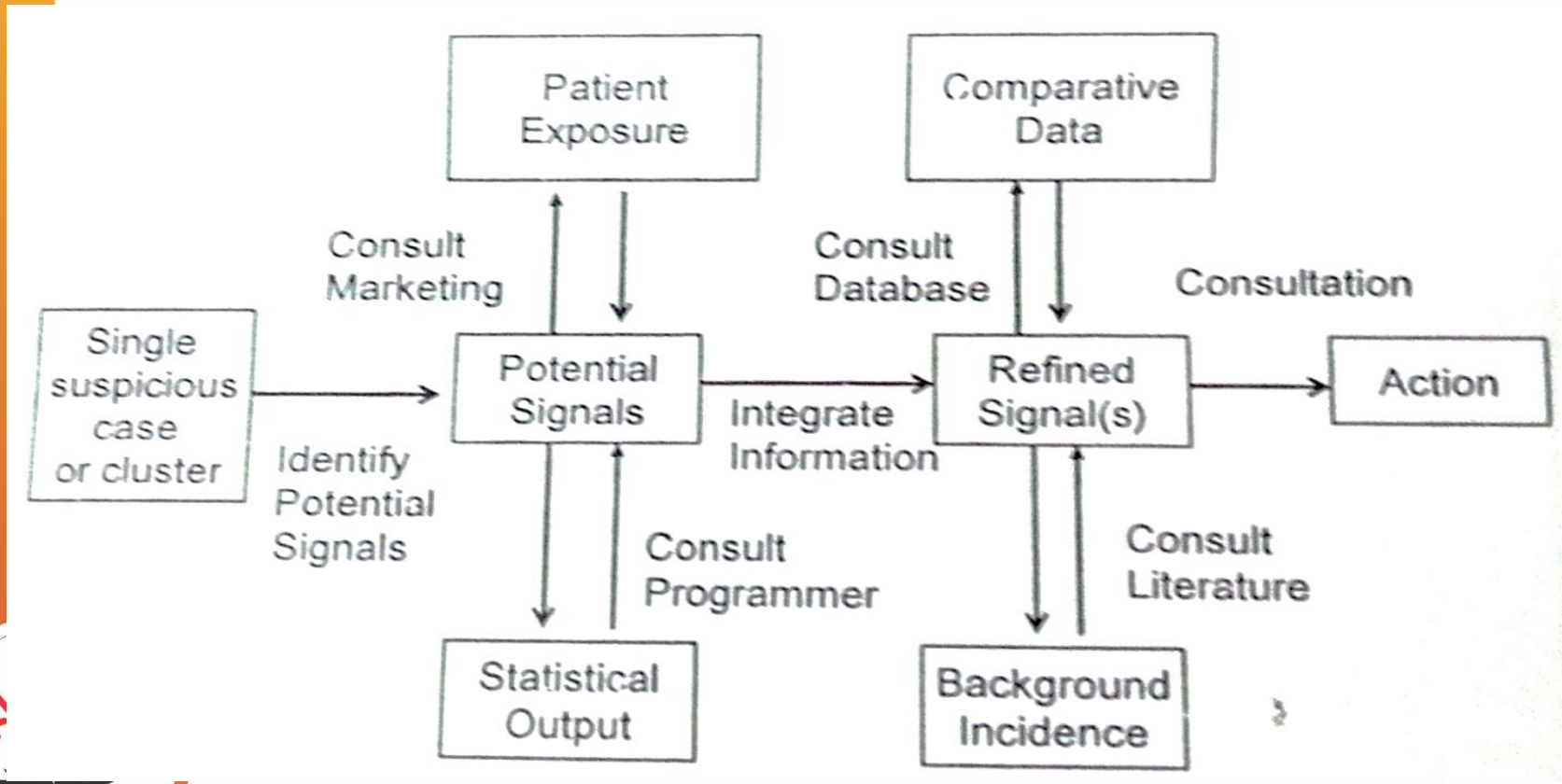
5) Recommendation for action

6) Communication

Types of Signal Detection

- Signal detection is of following two types.
- Clinical (Traditional – astute clinicians)
  - Individual case review
    - Unusual events in the target population
    - Unusual severity of a specific event
  - Periodic review of aggregate information
    - Frequency tables – Plain old counts
    - Increased frequency calculation
  - Case series analysis
- Data Mining
  - Statistical methods for disproportionality assessment
  - Caveat – non-intended for hypothesis testing

Signal Generation – The Traditional Method



Data Mining

In data mining, we detect rare unpredictable ADRs.

We detect interactions that are

- Drug-Drug based (OTC, Herbal, Traditional, etc...)
- Drug-Food based (supplements, etc...)
- Drug-Disease based
- We also identify the high-risk patients group. Plain old counts and frequencies are studied. Mathematical upon statistical i.e. 2x2 tables is used.

Investigating safety signals

Potential signals can be evaluated using more reliable data sources such as observational/pharmacoepidemiologic studies, additional randomized clinical studies, or mechanistic studies.

- Safety signals that warrant further investigation include
- New adverse events, not currently documented in the product label, especially if serious and in rare untreated populations.
- An apparent increase in the severity of an AE that is already included in the label.
- Occurrence of SAEs known to be extremely rare in the general population.
- Previously unrecognized interactions with other medicines, dietary supplements, foods, or medical devices.
- Previously unrecognized at-risk population, such as populations with specific genetic or racial predisposition or coexisting medical conditions.
- Confusion about a product's name, labeling, packaging, or use.
- Concerns arising from the way a product is used (e.g., adverse events seen at doses higher than normally prescribed, or in populations not recommended, in the label).
- Concerns arising from a failure to achieve a risk management goal.

Signal Analysis (1)

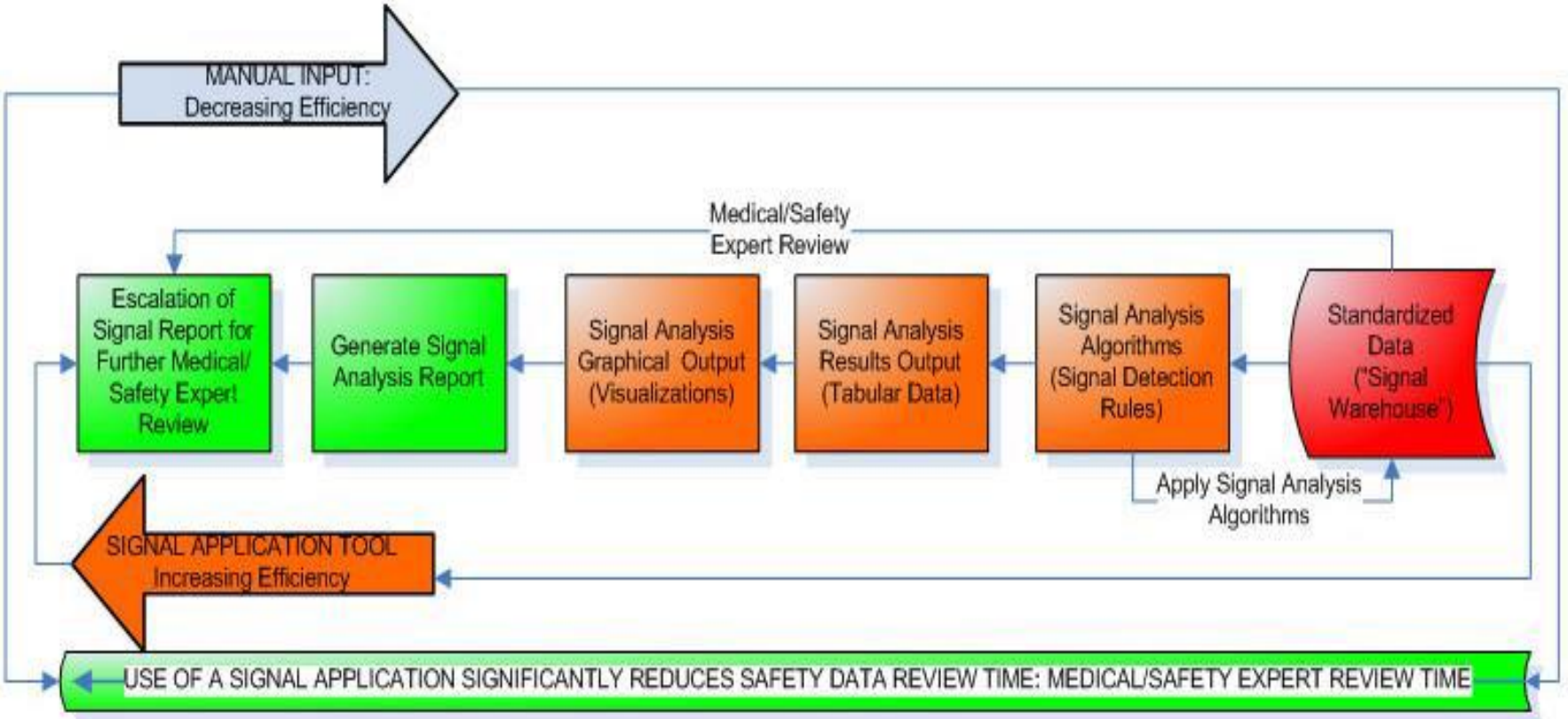
- Signal analysis procedures should be implemented during the pre- and post-approval phases of product development
- Standardized, methodical descriptive algorithms and appropriate statistical methods should be applied in screening of data, both pre and post market data, and should feed into an iterative benefit-risk assessment.
- Statistical signal analysis methods applied in spontaneous databases are considered exploratory and not confirmatory.
- Exploratory signal analyses of adverse event databases for hypothesis generation can be integrated into traditional medical review and the risk assessment process.

Signal Analysis (2)

A pre-market approval signal analysis process adds to the traditional review process for:

- Standardized routine signal detection and evaluation approach that is reproducible.
- Identification of potential or true signals, based on probable or possible association of an AE/ADR and the index product.
- Assessment of the medical significance of a signal and a signal strength (where quantified) and unexpectedness, along with review of reporter and company causality assessment.
- Evaluation of alternative explanations for causal association of a potential or true signal.
- Prioritization of potential or true signals, for review by medical/safety experts for further assessment, where warranted, to determine those of any or significant safety concerns.

A Schematic Representation of Increasing Efficiency Using a Signal Analysis Application and Decreasing Efficiency with Only Manual Input Process



Signal Analysis (3)

The role of a Signal Analyst or Safety Data Reviewer should include at a minimum the review and assessment of:

- SAEs,Discontinuation/dropout events (in clinical trials)
- Frequency or incidence of the events that are, or may be, causally related
- Dosage Analysis: Evaluation of the extent of exposure at relevant doses
- Other Dosage Analysis: Dose, plasma level, duration of exposure, etc.
- Adverse event profile of vulnerable populations such as: pediatric, elderly, pregnant women, etc.
- Adverse event profile of high-risk populationsCardiac events and related events
- Drug-drug interactions or potential interactions, other drug-related factors
- Demographic analyses, e.g., age, gender, ethnicity, race, etc.
- Concomitant medications burden
- Comorbidity burden
- Rare/sentinel events
- Events whose causality are associated with the mechanism of action or pharmacology of the index drug (Type A events)
- Events not associated with the mechanism of action or pharmacology of the index drug (Idiosyncratic Type B events, Type C events, etc.)
- All other relevant safety data

Signal Evaluation

- The process of Signal evaluation involves analyzing all the data available considering the strength of evidence from the cases, clinical relevance and previous awareness.
- It also includes:
  - Eliminate known issues
  - Identify signals of concerns
  - Creating case series
  - Formulation of hypothesis
  - Assess causal likelihood

Signal Communication

- All identified signals require some action to be taken.
- No signal can be ignored.
- Signal identified need to be communicated to all concerned stakeholders
- Legal liability needs to be checked.

Conclusion

Signal management process culminates in either of the following ways:

- Signal closed (there is no signal or no further immediate action)
- Signal closed but requires follow-up (FU) (if some follow-up other than monitoring is required (e.g. check next PSUR submission…), the nature of the follow-up is clearly mentioned in the tracking table and the issue is flagged as “Closed+FU”
- Signal monitored -available information is currently limited (e.g. there are a small number of cases); new cases reported to EudraVigilance will need to be evaluated).
- Signal ongoing (further analyses or verifications are required before a conclusion can be reached. The signal is discussed at the next relevant surveillance meeting
- Signal validated - Rapporteur needs to be informed (a proposal for a regulatory action to be performed by the Rapporteur with the appropriate timeframe should be suggested, e.g. cumulative review to be requested in next PSUR).

Conclusion (2)

- Thus, signal detection is an essential public health activity.
- Signals are not necessarily risks; every signal must be evaluated for its potential to be a RISK.
- Effective signal evaluation requires a focus on key issues of concern.
- To meet increasingly stringent regulatory agency requirements and minimize liability, companies must develop more effective and simpler methods of signal evaluation

Questions?