Detection and evaluation of drug safety signals in post marketing phase



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Overview of Lifecycle Signal Management

- Public and media pressures
- Exactly what is a ‘signal’?
- How is a signal identified?
- How do we perform signal management



Drug Safety and the Media……

Drug Approval Trends at the FDA and EMEA: Process improvements, heightened scrutiny and industry response

Drug safety has become a major industry concern following the market withdrawal of Merck's Vioxx in 2004 and several other discontinuations of COX-2 inhibitors. Although adverse reactions were previously considered a relatively minor risk compared to a drug's wider benefit, both newly approved and established drugs are now under intense scrutiny. Drug

MORE NEWS

- UPDATE 2-Pfizer halts enrollment in lung cancer trial
  Friday, 9 Oct 2009 04:46pm EDT

By Lewis

NEW YO
halted p
lung can

drug, figitumumab, for safety reasons
Friday.

FDA's Biggest Blunders

The Food and Drug Administration's sordid drug recall past.

By Jim Kling for MSN Health & Fitness

Medically Reviewed By: Pat F. Bass III, M.D., M.S., M.P.H.



1 | 2 | Next >

Merck's Vioxx, a nonsteroidal anti-inflammatory (NSAID) painkiller, made headlines in 2004 when the company voluntarily withdrew it from the U.S. market following reports of increased rates of strokes and heart attacks in patients taking the drug chronically. Vioxx was the most famous of more than a dozen drugs withdrawn from the market since 2000.

FDA significantly restricts access to the diabetes drug Avandia



ed that it will significantly restrict
with Type 2 diabetes who
restrictions are in response to
ch as heart attack and stroke, in

Preparation for MHRA Inspection

Regulatory Inspections by the MHRA/FDA: assistance available from the Research Department

The MHRA now has a large team of inspectors who are visiting NHS Trusts for routine systems inspections and triggered inspections of research facilities and individual trials. In the period of 6 months since November 2006, we shall have had 5 inspections/accreditation visits of individual trials.

Need of pharmacovigilance after regulatory approval

The populations exposed to any drug during the post authorisation period differ from those studied during the development of the medicinal product.



In daily practice…..

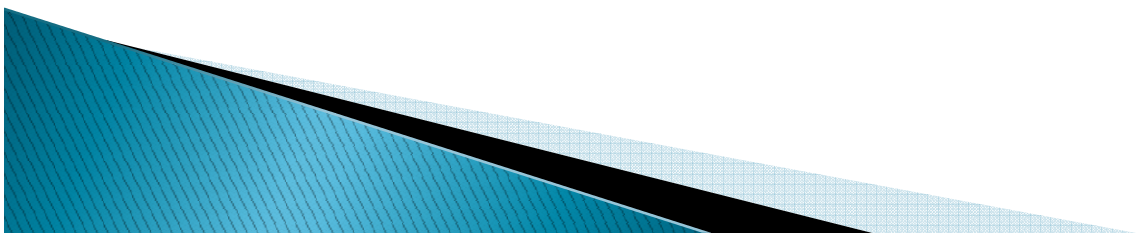
- Patients are not selected
- Large and diverse populations
- Therapy duration vary
- Underlying diseases/concomittant medical conditions
- Poly pharmacy

Continue…

- New information on the benefits and risks of any drug may be generated at any time after marketing approval has been granted

It is important

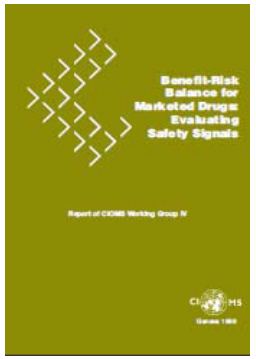
- To continuously monitor the safety of any medicinal product during its market life;
- To continuously assess its risk-benefit profile in order to guarantee patient's safety.



Definition of a 'Signal' ?

MHRA

U.S. Department of Health & Human Services
FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health



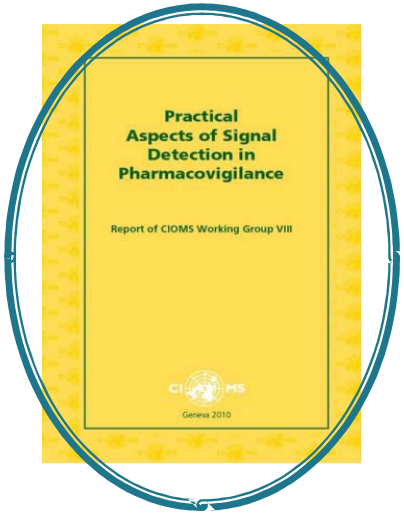
BfArM



European Medicines Agency

World Health Organization

NEW →

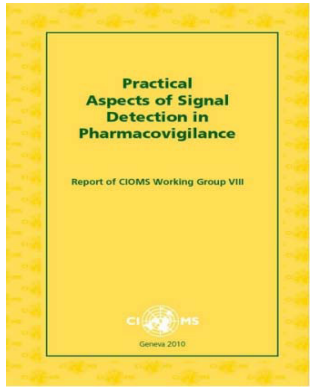


Health Canada
www.hc-sc.gc.ca



CIOMS VIII – New Signal Definition

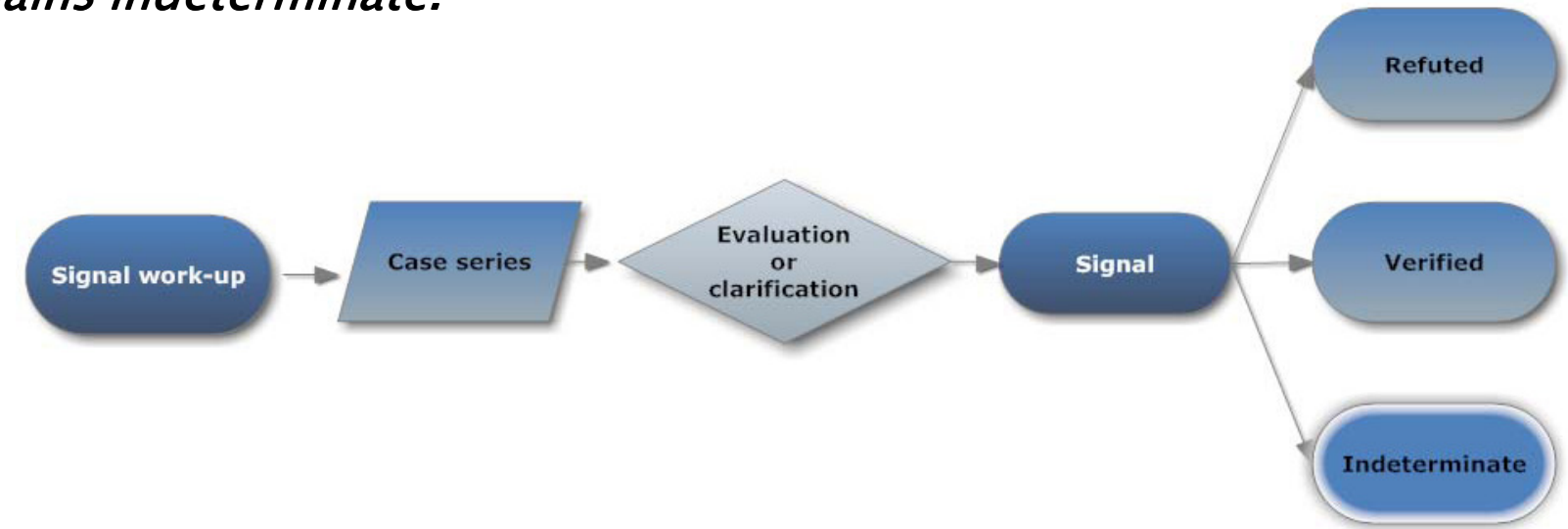
Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, *between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be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



Safety Finding (message) ≠ Signal

So a Signal requires:

❖ an initial *evaluation or clarification step to determine whether the* case series, less frequently one single case, that has raised attention will require further evaluation. Once this step has been completed , the safety finding becomes a signal which can be *verified, refuted or remains indeterminate.*



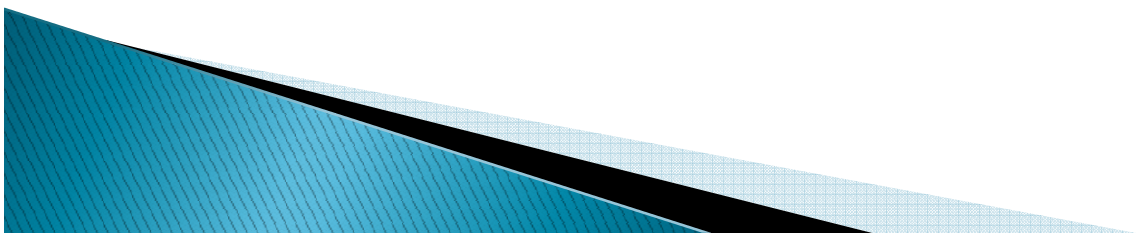
In summary, a safety Signal is……

- Information that arises from one or multiple sources (including observations and experiments)
- Suggesting a new potential 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 of sufficient likelihood to justify verificatory action.



Sources of signals

- Pre-clinical data (animal toxicology, pharmacology)
- Clinical trials data (phases I – IV)
- Spontaneous reports (company database, regulatory databases)
- Published literatures
- Epidemiology/Registries/Prescription event monitoring studies
- Competitor data



Sources of Signals Vary During the Product Lifecycle

Pre clinical development	Clinical Development	1st years after launch	Mature Product
In vitro studies Chemistry ADME* Target receptors Transporters *In vivo studies* Animal	Human studies •Adverse events •Laboratory data •Biometrics •PK Animal studies *In vitro studies*	*Human studies* •Phase IIIb/IV •New indications Spontaneous case reports Published literature Epidemiology	Human studies •Adverse events •Laboratory data •Biometrics •PK Animal studies *In vitro studies*

*Absorption, distribution, metabolism, excretion

Signal Management Process

- signal detection;
- signal validation;
- signal analysis and prioritization;
- signal assessment;
- recommendation for action
- exchange of information.



How is a signal identified?



Hunts Needle in a

HOW LONG does it take to find a
stack? Jim Moran, Washington, D
recently dropped a needle into a
hay, hopped in after it, and began a
for (a) some publicity and (b) t
found the former, Moran abandone

Methods for identification of signals?

Traditional methods (Qualitative)

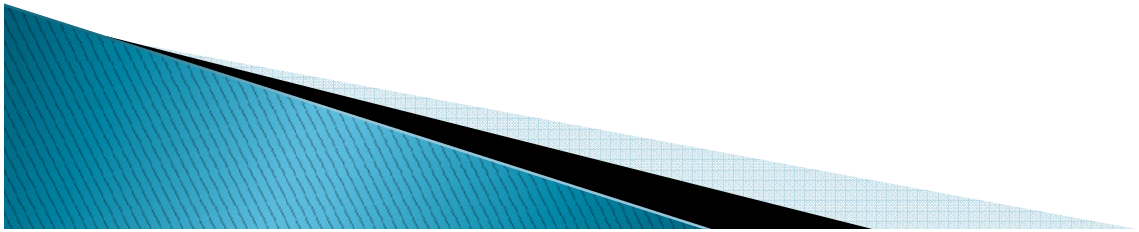
•Review of individual cases (index case or striking case method) or case series in a PVG safety database or in published medical or scientific literature.

•Aggregate analyses of case reports using absolute case counts, simple reporting rates or exposure adjusted rates.

Data mining methods (Quantitative)

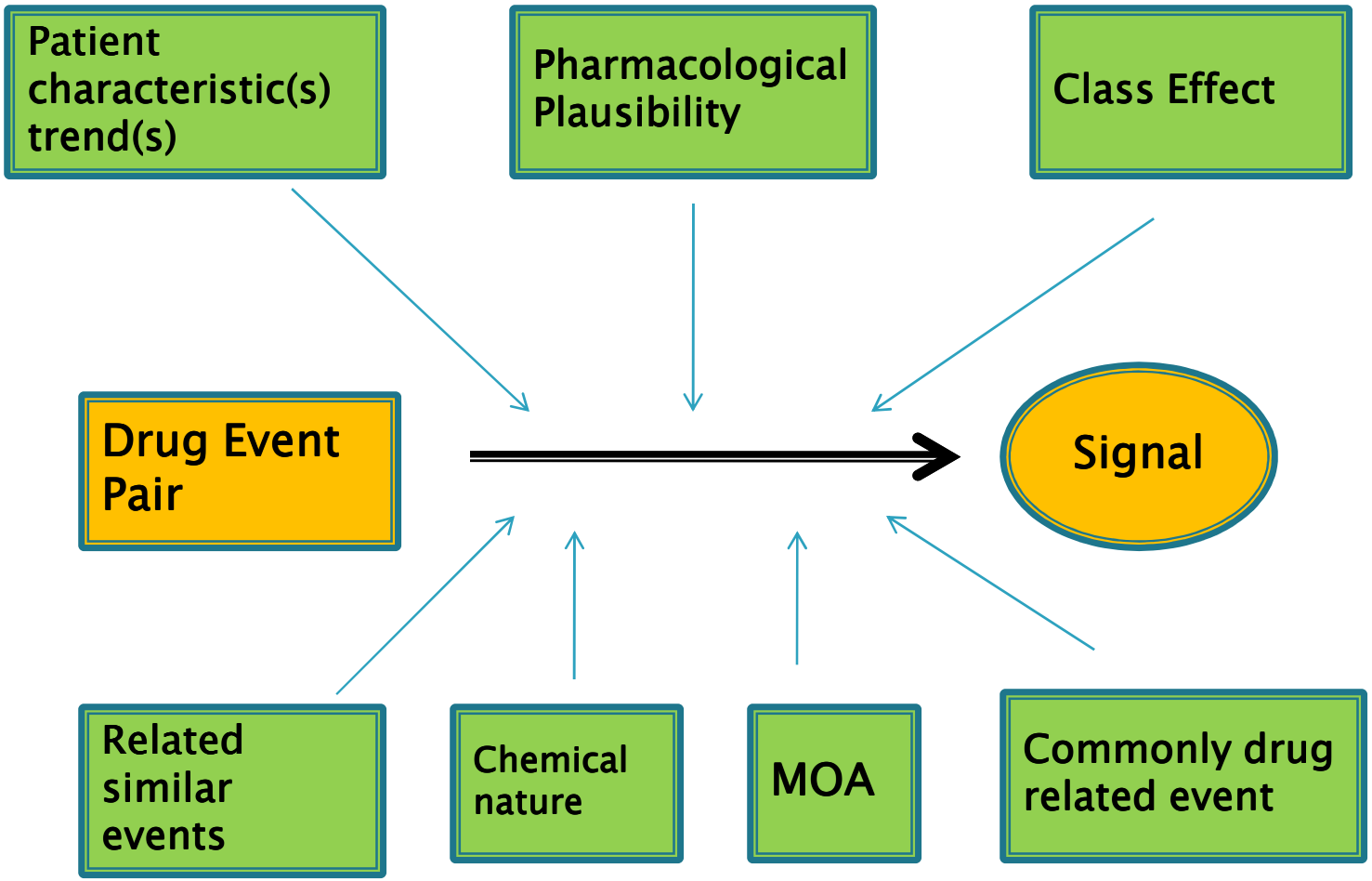
•Identify drug-event combinations that are disproportional to pooled or overall distribution in the background dataset

• Does not infer causality only a higher frequency of reporting than expected

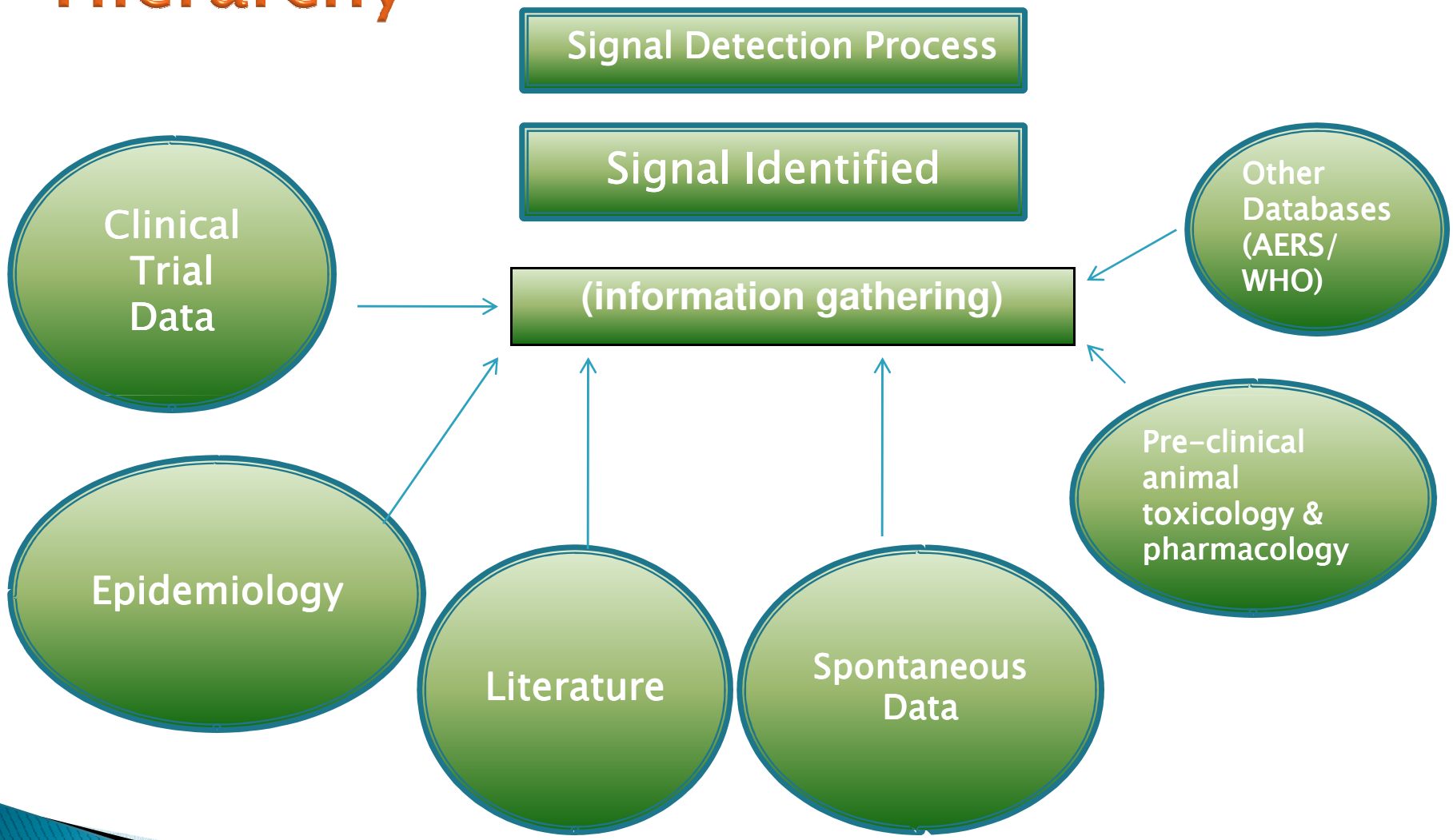


Factors to Consider in Signal detection

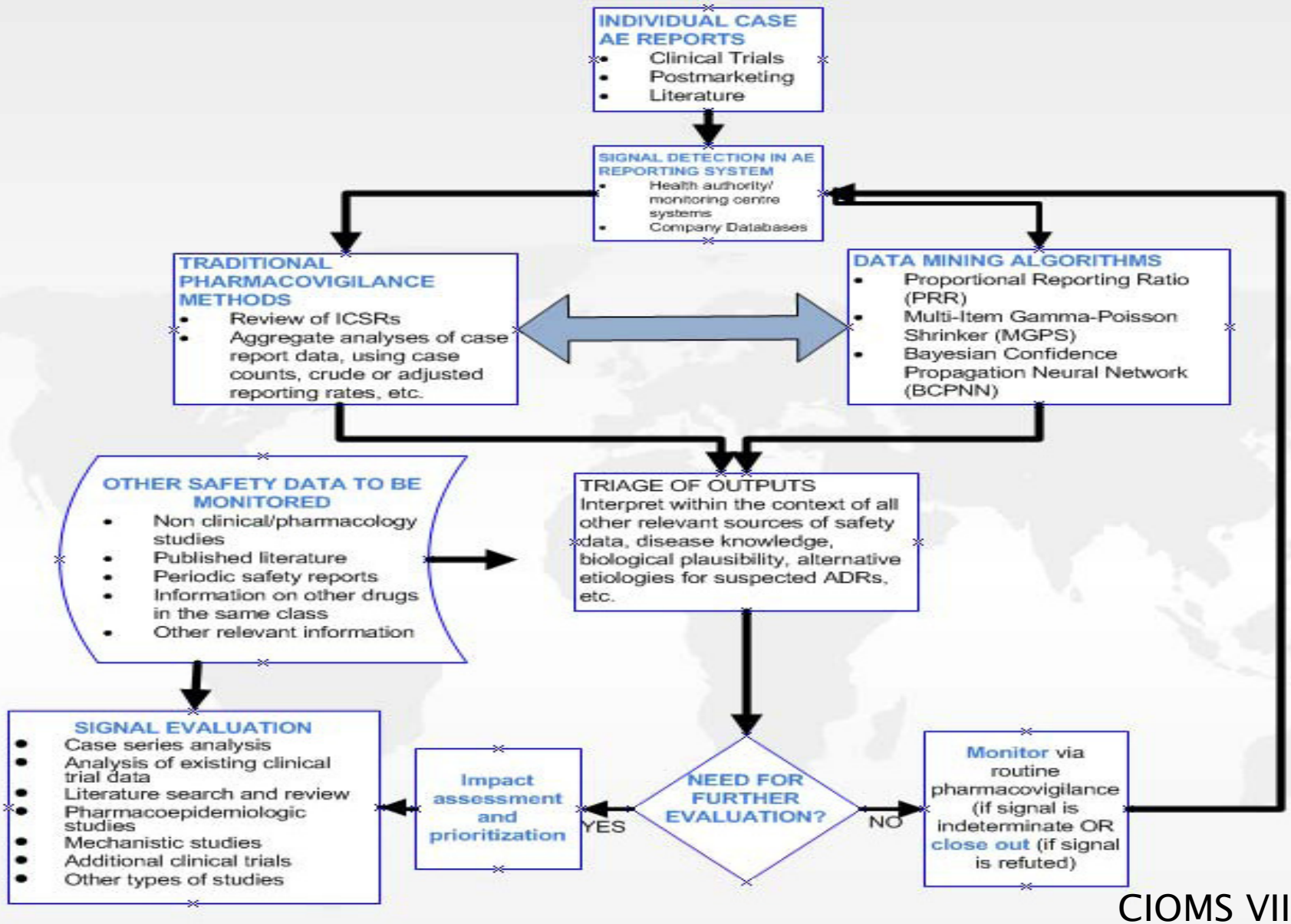
Considerations for when a drug event pair is a signal



Evaluating Signals Using Evidence Hierarchy



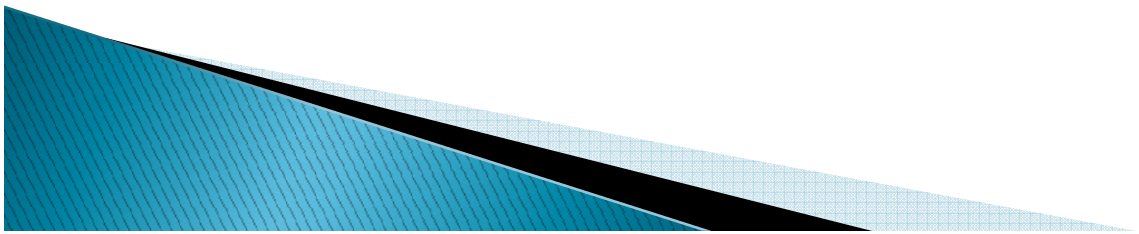
Signal Management Process



CIOMS VIII

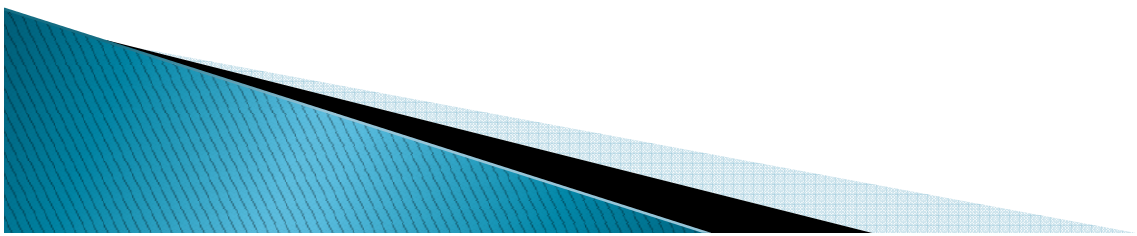
Is There Anything New?
Is this a Public Health Issue?

- Unidentified/unlabeled
- Change of frequency
- Change of severity
- New risk factors
  - Serious, severe, or sustained?
  - Who, and therefore how many will be affected?



Possible Actions Resulting from Signal Evaluation

- No evidence of a causal relationship
  -No action, document
- Insufficient information: Need to continue to monitor and revisit
  -Plan to gather more information
  -Targeted follow up questions for spontaneous reports
  -Design studies (Pharmacoepidemiological studies, clinical studies, drug interaction studies)
- Milestone reviews- when significant information available



Risk Management – Devices

Strategies include:

- Risk Communications
- Labelling changes
- Requests for safety information
- Reclassification of devices
- Recall – monitoring strategies
- Product withdrawal



Thank You

