Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance and complementary medicines

Regulatory Requirements

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TGA Health Safety Regulation

Presentation overview

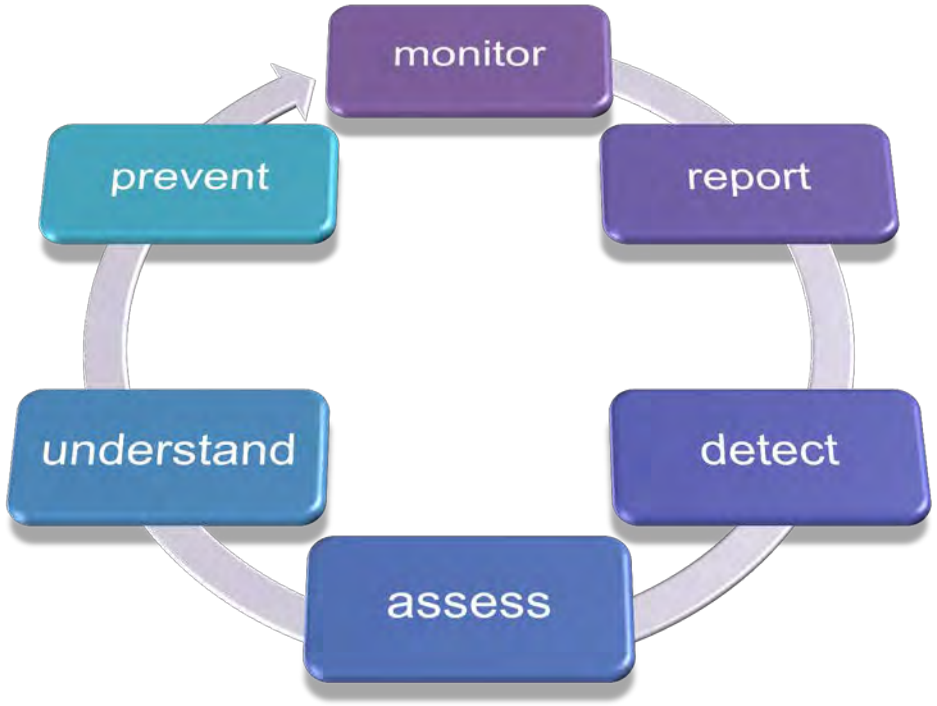
- Pharmacovigilance basics – sponsor obligations
- Complementary medicine safety – Regulatory perspective
- Special considerations for complementary medicine pharmacovigilance

Pharmacovigilance basics

The WHO defines pharmacovigilance as '*the science and activity related to:*

- *detecting,*
- *assessing,*
- *understanding, and*
- *preventing*

adverse effects and other medicine-related problems.'



Legal obligations and penalties

Sponsors **must** notify the TGA of:

- Any serious adverse event
- Any significant safety issue
- A change in the benefit-risk balance
- Information which indicates the safety, efficacy or quality is unacceptable

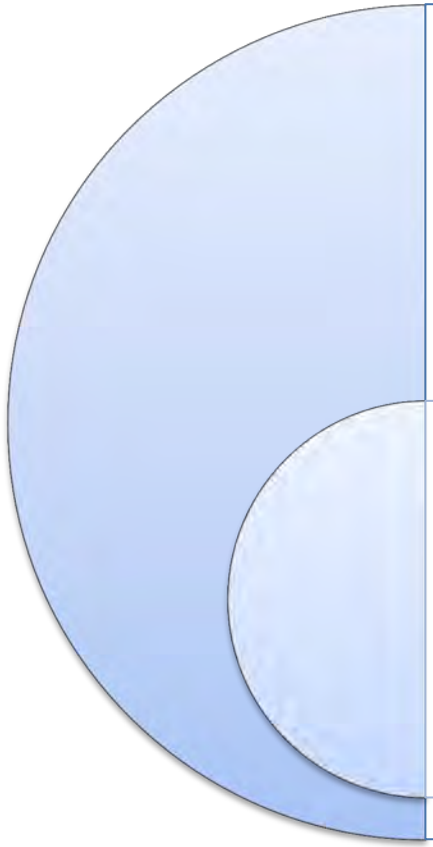
Penalties for non-compliance

The *Therapeutic Goods Acts 1989* specifies criminal and civil penalties for failing to notify adverse events:

Section 29A – Criminal penalties:
12 months imprisonment and/or
1,000 penalty units (p.u.; $210,000)

Section 29AA – Civil penalties:
≤3,000 p.u. (individual; $630,000) or
≤30,000 p.u. (body corporate; $6.3M)

Pharmacovigilance obligations – contact person



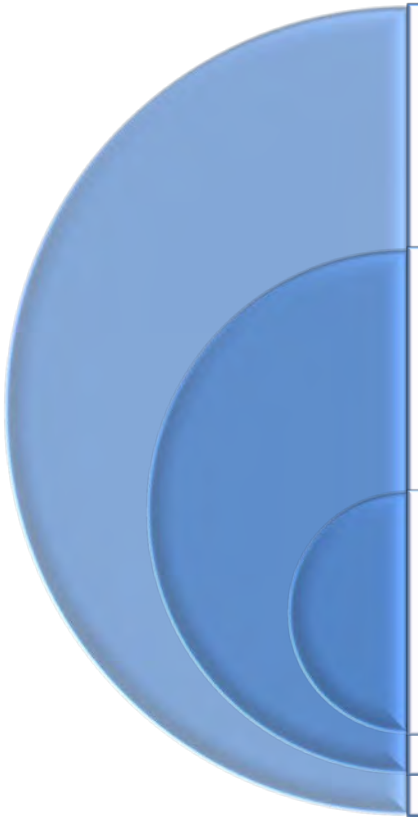
Sponsors must have an Australian Pharmacovigilance contact person

- Provide name and contact details within 15 days of entry of first medicine
- Maintain current details (notify us within 15 days of any changes)

The Australian Pharmacovigilance contact person:

- Must reside in Australia
- Should have a sound understanding of Australian pharmacovigilance reporting requirements

Pharmacovigilance obligations – reporting timeframes



Serious Adverse Reactions ≤15 calendar days	• Expected or unexpected • Adverse reactions that occur in Australia • Literature reports of Australian cases • Relevant follow up information
Significant safety issues ≤72 hours	• Indicate points of concern, and whether you plan to take any actions
Non-serious adverse reactions (reporting not required)	• Must keep records and provide them to TGA if requested • Must report if they impact on benefit-risk balance

Note: Spontaneously reported AEs are considered an adverse reaction, even if causality is unknown or unstated

What is a serious adverse event?

≤15 days

- results in death
- is life-threatening
- results in inpatient hospitalisation or prolonged hospitalisation
- results in persistent or significant disability or incapacity
- is associated with a congenital anomaly or birth defect
- is a medically important event or reaction.

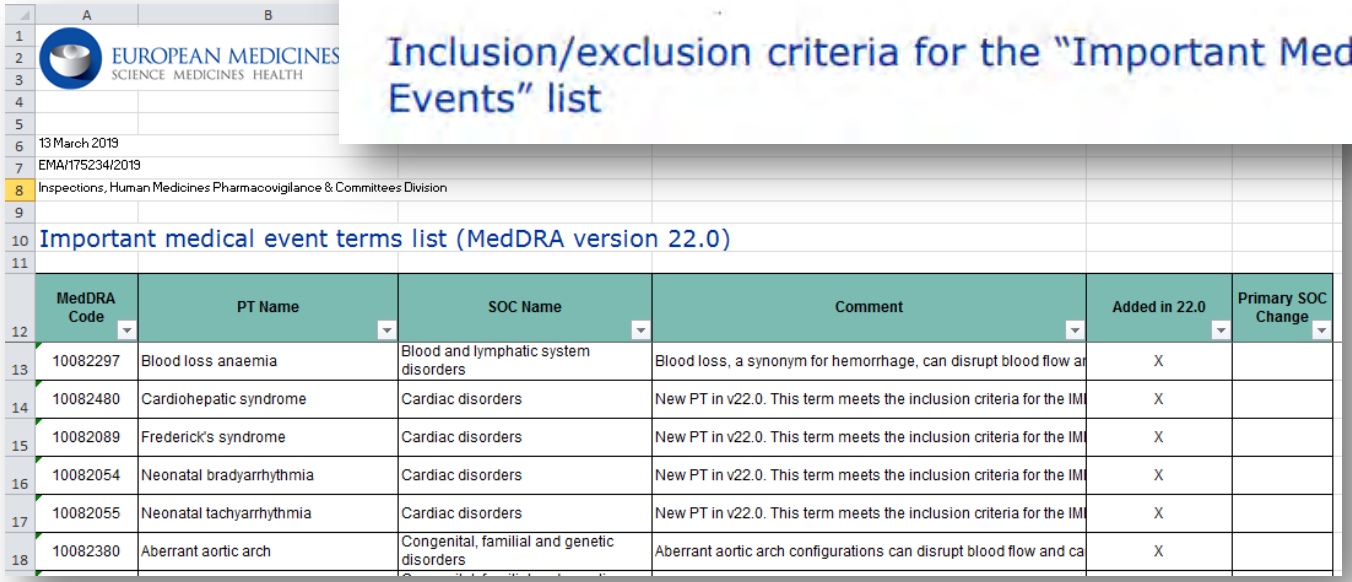
What is a ‘medically important’ event or reaction?

- Require judgement
- Resources available to assist in defining criteria
- Unsure?
  - Recommend conservative assessment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 March 2019
EMA/825370/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Inclusion/exclusion criteria for the “Important Medical Events” list



EUROPEAN MEDICINES
SCIENCE MEDICINES HEALTH

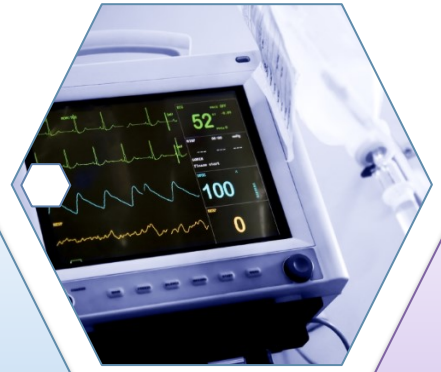
13 March 2019
EMA/175234/2019
Inspections, Human Medicines Pharmacovigilance & Committees Division

Important medical event terms list (MedDRA version 22.0)

MedDRA Code	PT Name	SOC Name	Comment	Added in 22.0	Primary SOC Change
10082297	Blood loss anaemia	Blood and lymphatic system disorders	Blood loss, a synonym for hemorrhage, can disrupt blood flow ar	X	
10082480	Cardiohepatic syndrome	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IM	X	
10082089	Frederick's syndrome	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IM	X	
10082054	Neonatal bradyarrhythmia	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IM	X	
10082055	Neonatal tachyarrhythmia	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IM	X	
10082380	Aberrant aortic arch	Congenital, familial and genetic disorders	Aberrant aortic arch configurations can disrupt blood flow and ca	X	

‘Medically important event’ – examples

Vital organ failures/ insufficiency



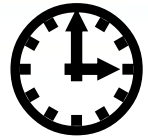
Terms for pregnancy with contraceptive (lack of efficacy/ interference)

Choking (if serious)

Immune disorders

e.g. anaphylaxis; severe urticaria/ angioedema

What is a significant safety issue?



≤72 hours

"New safety issue or validated signal considered by you in relation to your medicines that requires the urgent attention of the TGA"

- Changes in the nature, severity or frequency of known serious adverse reactions which are medically significant
- Detection of new serious adverse reaction that may impact on the safety or benefit-risk balance of the medicine
- Detection of new risk factors for the development of a known adverse reaction that may impact on the safety or benefit-risk balance of the medicine
- Cluster of adverse reactions assessed to suggest a quality defect issue that may have implications for public health
- Safety related actions by comparable international regulatory agencies

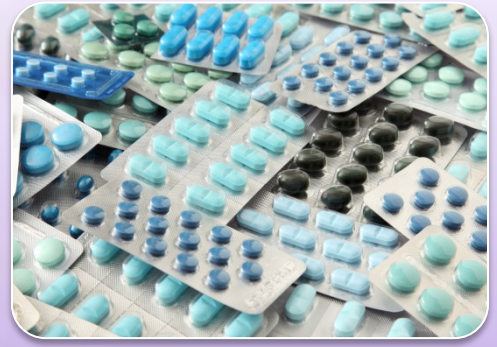
Pharmacovigilance basics – sponsor obligations

Complementary medicine safety – Regulatory perspective

Special considerations for complementary medicine pharmacovigilance

Registered *vs* listed medicines

Safety & efficacy from traditional use or clinical trials (usually small)
Products not evaluated by TGA
Frequently combinations of ingredients
Preparation and dose of different active ingredients may vary



Safety & efficacy from clinical trials (usually large)
Fully evaluated by TGA
Generally single active ingredients, or studied combinations
Preparation and dose of active ingredient supported by trials

Complementary medicines

Listed complementary medicines

Permitted ingredients

- Low risk ingredients
  - *For herbal ingredients, may be whole or part of plant*
- May have requirements relating to
  - *Route of administration*
  - *Dose or concentration limits*
  - *Preparation type*
  - *Label warnings*

Permitted indications

- Health maintenance or enhancement
- Prevention of non-serious deficiency
- Refer to certain non-serious, self-limiting diseases, ailments, defects or injuries

Permissible ingredients *vs.* products

The permissible ingredients list is dynamic

- Ingredients may be added or removed
- Requirements may be added or varied
- Usually at ingredient level, not preparation type

Sponsors are responsible for the safety of their **products**

- Sponsors must monitor the safety of their products
- Sponsors must comply with the requirements of the *Permissible Ingredients Determination*
- Should consider if factors such as preparation or combination will impact safety

Benefit-risk of complementary medicines

- To maintain an acceptable risk-benefit ratio, risks must be minimal, i.e.:
  - Non-serious
  - Reversible
  - Mild
- More serious risks may be acceptable if they are rare and can be adequately mitigated, e.g.
  - Label warning
  - Restrictions on dose, population etc

Pharmacovigilance basics – sponsor obligations

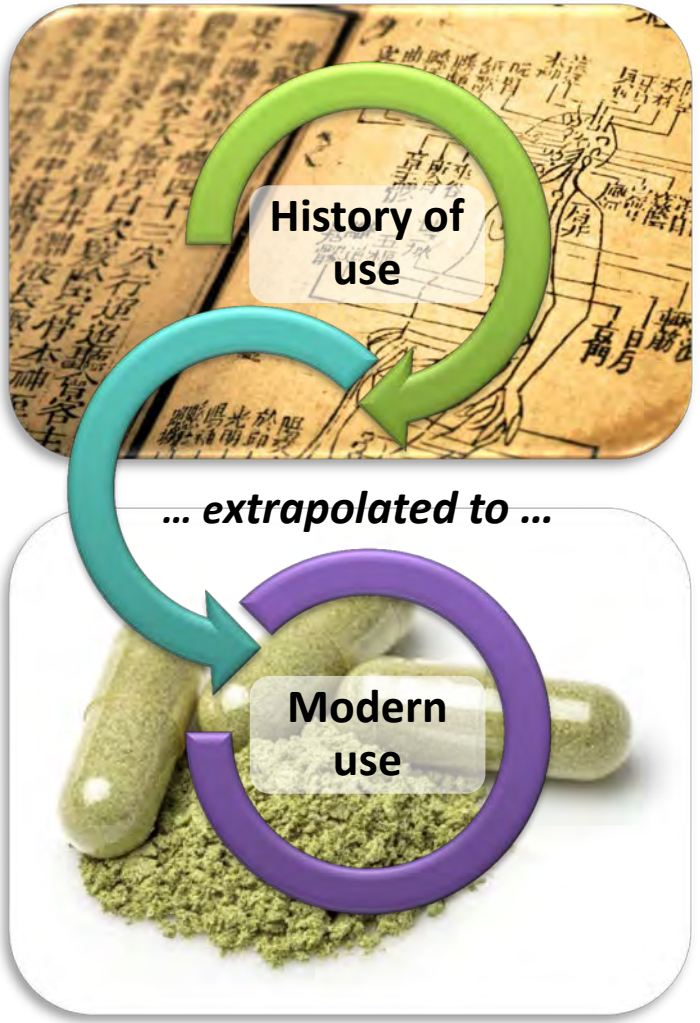
Complementary medicine safety – Regulatory perspective

Special considerations for complementary medicine pharmacovigilance

Pharmacovigilance for complementary medicines

- Regulatory framework for listed medicines has areas of uncertainty, especially for grandfathered ingredients
- Key considerations for extrapolations from traditional use or small clinical trials:
  - Limitations
  - Relevance
  - Dose
  - Preparation
  - Rare adverse events

Therefore, robust post-market monitoring is required



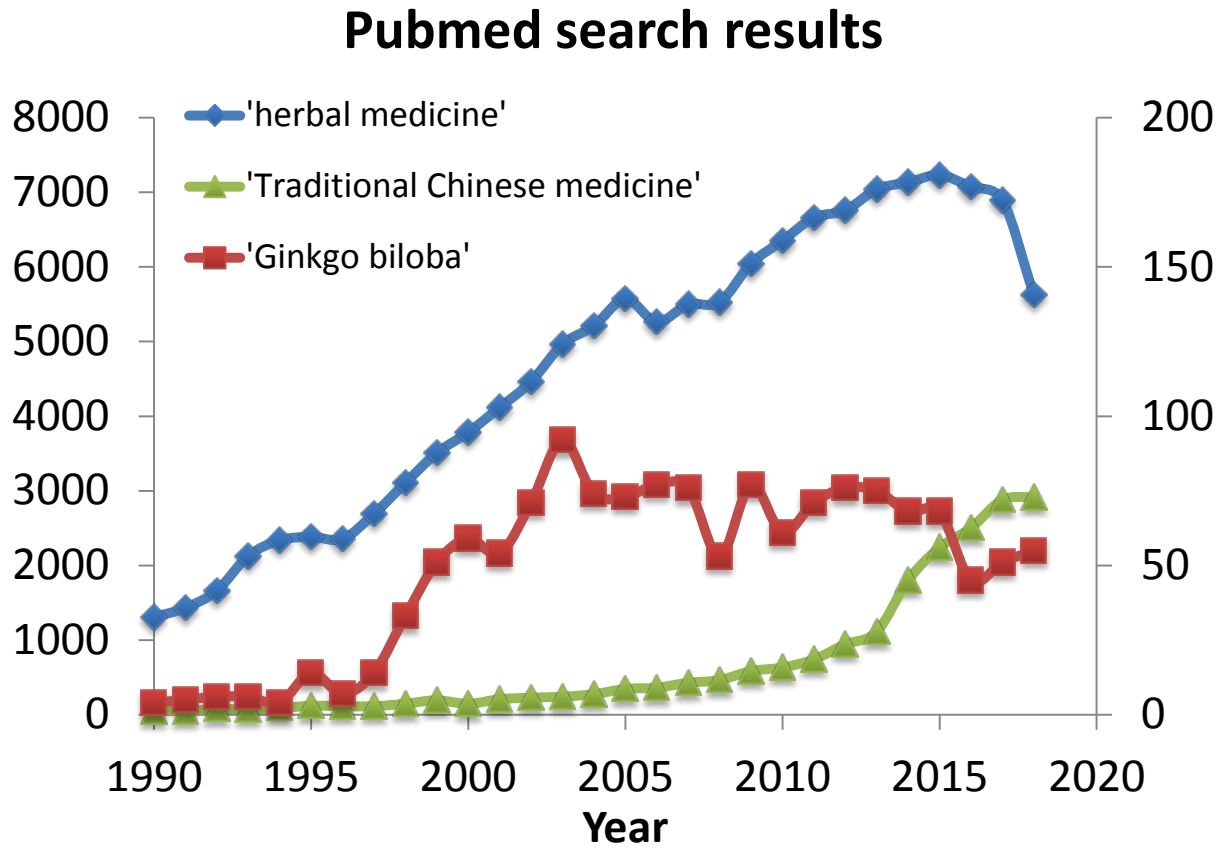
Extrapolating safety data

Limitations	• Is the data sufficient and of high quality? • What about long term safety concerns (e.g. carcinogenicity or developmental effects)?
Relevance	• Is the combination of ingredients in a product supported by traditional use? • Could some ingredients potentiate or exacerbate another ingredients adverse events?
Dose	• Does the maximum daily dose exceed traditional doses?
Preparation type	• What extraction methods were used traditionally? • Could a modern extraction method (and ratio) elicit a different safety profile?
Rare adverse events	• Rule of 3 – to detect a rare adverse event (1/1000), clinical trial would need *n* = 3000

Role of scientific literature – monitor and detect

- Increased number of publications due to research interest:
  - Clinical trials
  - Case studies
  - Retrospective studies/ cohort studies
  - Mechanistic studies
- Potential source of:
  - Australian adverse events from case studies
  - Significant safety issues

➢ ***Emerging evidence for safety and efficacy***



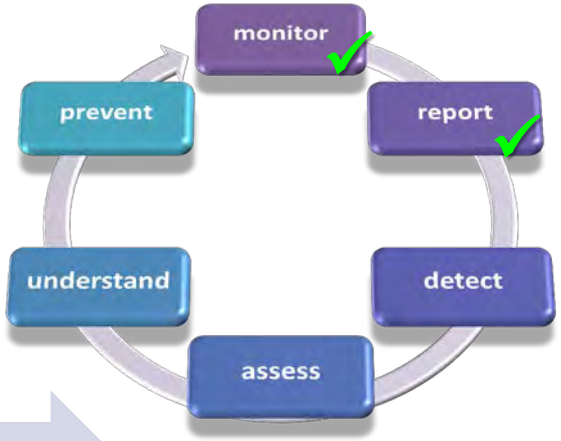
- ***Filters: 'human' and 'English language'***
- ***Ginkgo Bilboa data on secondary axis***

Challenges for post-market monitoring

- Under-reporting
- Potential link between product and AE not identified – believed to be safe
- HCPs not aware of use
- Concerns about regulatory action e.g. reduced availability
- Identifying source of safety issue – quality problem or inherent safety?

Pharmacovigilance is more than just reporting

Assessing, understanding and preventing adverse events



Signal detection

- Signals may arise from multiple sources
- Need to conduct cumulative reviews of cases

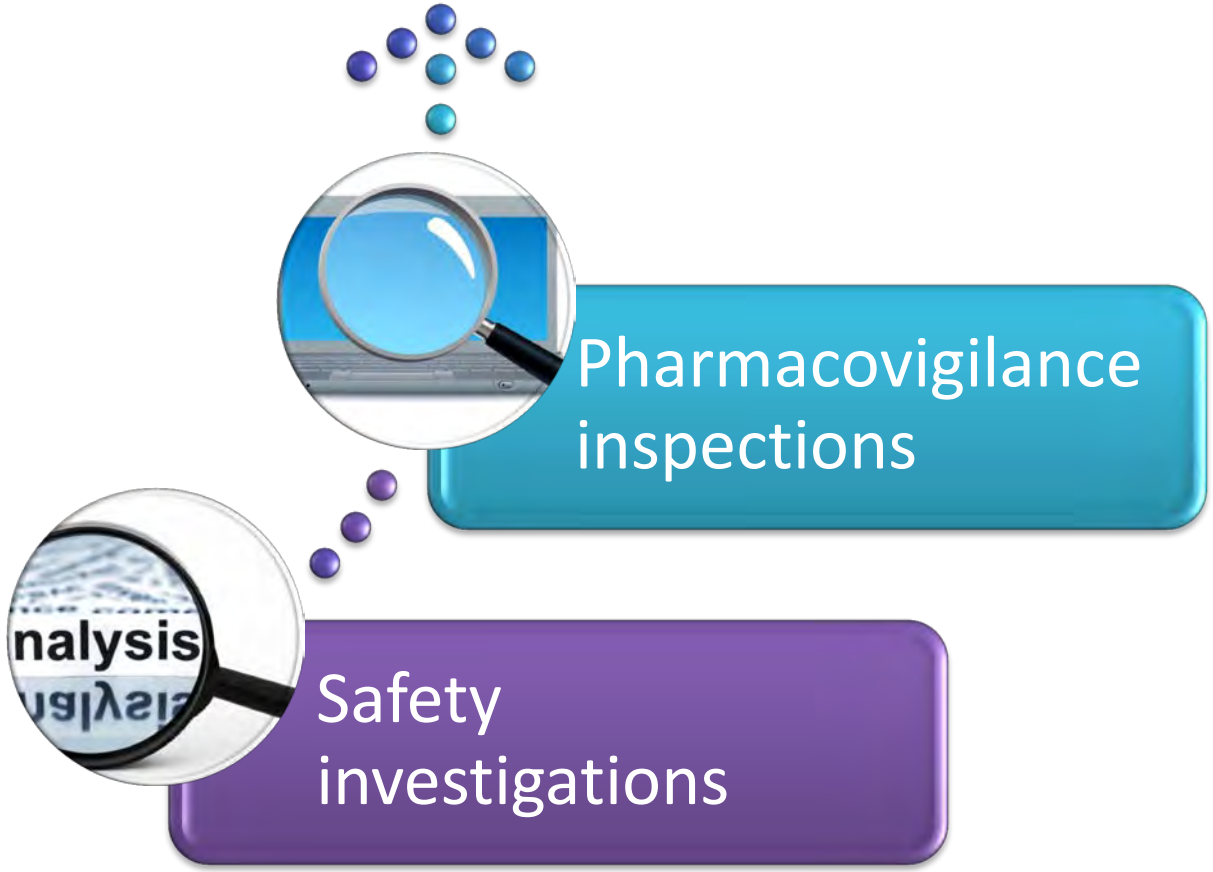
Signal investigation

- Actively investigate signals to identify any causal links
  - ➲ *Verify or refute the signal*

Action

- Is action warranted based on your risk assessment?
- Notify TGA if there is a change in risk-benefit, including proposed actions

How is compliance with PhV requirements assessed?



- Safety investigations may identify:
  - Under-reporting of serious AEs
  - Misclassification of seriousness
  - Lack of signal investigation
- Pharmacovigilance inspections
  - Complementary medicine sponsors are in scope
  - Risk-based prioritisation

Summary and conclusions

Pharmacovigilance requirements apply to complementary medicine sponsors.	• Significant penalties for non-compliance • Know your reporting requirements!
Listed complementary medicines are low risk products.	• Adverse events should be considered in the context of risk: benefit • There are areas of uncertainty
Listed medicines have areas of uncertainty	• A robust pharmacovigilance system is required to ensure acceptable safety, efficacy and quality
Monitor and report adverse events	• Spontaneous reports and literature are important sources of information
Pharmacovigilance is more than just monitoring and reporting	• Detect and investigate safety signals • Propose and take appropriate actions to prevent adverse events

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