Pharmacovigilance and complementary medicines

Regulatory Requirements

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Presentation overview

Pharmacovigilance basics – sponsor obligations

Complementary medicine safety – Regulatory perspective

Special considerations for complementary medicine pharmacovigilance
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

<table>
<thead>
<tr>
<th>Sponsors must have an Australian Pharmacovigilance contact person:</th>
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<tbody>
<tr>
<td>• Provide name and contact details within 15 days of entry of first medicine</td>
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<tr>
<td>• Maintain current details (notify us within 15 days of any changes)</td>
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<table>
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<tr>
<th>The Australian Pharmacovigilance contact person:</th>
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<tr>
<td>• Must reside in Australia</td>
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<tr>
<td>• Should have a sound understanding of Australian pharmacovigilance reporting requirements</td>
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## Pharmacovigilance obligations – reporting timeframes

<table>
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<tr>
<th>Adverse Reaction Type</th>
<th>Timeframe</th>
<th>Requirements</th>
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| **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?

- 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.

≤15 days
What is a ‘medically important’ event or reaction?

- Require judgement
- Resources available to assist in defining criteria
- Unsure?
  - Recommend conservative assessment
‘Medically important event’ – examples

- Vital organ failures/insufficiency
- Immune disorders e.g. anaphylaxis; severe urticaria/angioedema
- Terms for pregnancy with contraceptive (lack of efficacy/interference)
- Choking (if serious)
What is a significant safety issue?

“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

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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
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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 $n = 3000$

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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

Pubmed search results

- 'herbal medicine'
- 'Traditional Chinese medicine'
- 'Ginkgo biloba'

• Filters: ‘human’ and ‘English language’
• Ginkgo Biloba data on secondary axis

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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