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Pharmacovigilance – a regulator's perspective

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UTS *Molecule to Market* – 13 October 2021

TGA Health Safety Regulation

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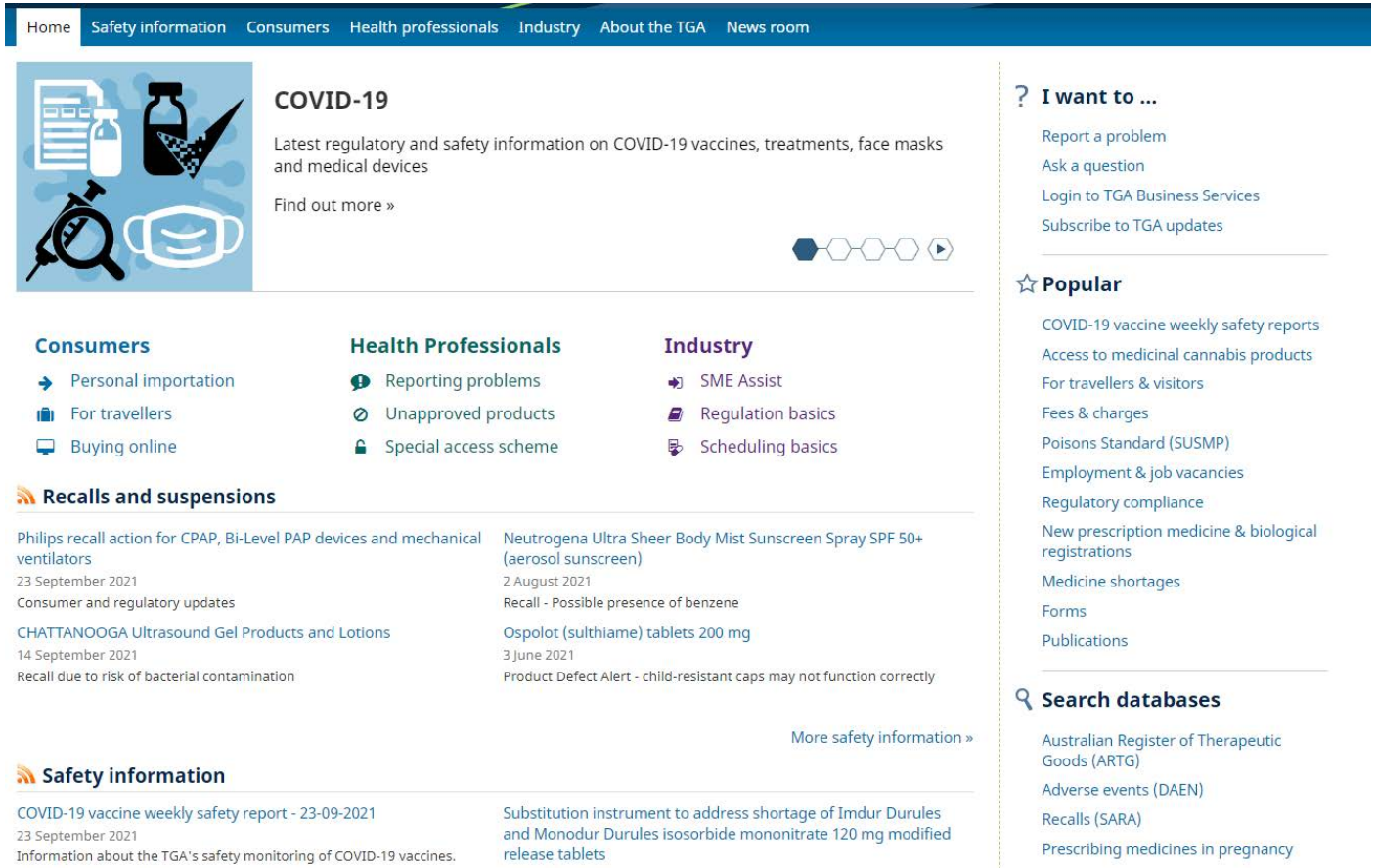
Overview

- Who are we and what do we do?
- What is pharmacovigilance?
- Pre-market pharmacovigilance
  - Risk Management Plans
    - Provisional registration status
    - Black triangle scheme
    - Products used for COVID-19
- Post-market pharmacovigilance
  - Adverse event reporting
  - Signal detection and investigation
  - Pharmacovigilance inspection

Who are we and what do we do



What do we do for pharmacovigilance

- Monitor the benefit-risk profile of medicines throughout the product lifecycle.
- Pharmacovigilance activities broadly fall into two categories:
  - **pre**-market
  - **post**-market.

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What is pharmacovigilance?

World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

Regulation and Prequalification

Incidents and SF | Laboratory Networks and Services | **Pharmacovigilance** | Regulatory convergence & networks | Regulatory systems strengthening | Facilitated Product Introduction

- **Pharmacovigilance**
  - Vaccine Safety Net
  - Information for general public
  - Information for health professionals

What is Pharmacovigilance?

Medicines and vaccines have transformed the prevention and treatment of diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.

All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Certain side effects may only emerge once these products have been used by a heterogenous population, including people with other concurrent diseases, and over a long period of time.

Pre-market pharmacovigilance

- Risk Management Plans (RMPs)
  - Sponsor: develop, maintain and implement RMP
  - TGA: evaluate RMP and make recommendations for improvement

Risk Management Plans (RMPs)

- Summary of Safety Concerns
- Pharmacovigilance Plan
- Risk Minimisation Plan

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Australian context

- A diverse population
- Geographic distance
- Levels of governments
- A unique healthcare system

Pharmacovigilance Plan

- Routine pharmacovigilance
  - Collection, follow-up and reporting of spontaneous adverse events.
  - Analysis of data and reporting in Periodic Safety Update Reports (PSURs).
  - Expedited summary safety reports for products used in COVID-19 pandemic
  - Provisional registration for medicines and biologicals with limited safety evidence requires close monitoring and confirmatory data on safety.
  - Black triangle scheme.

Pharmacovigilance Plan (continued)

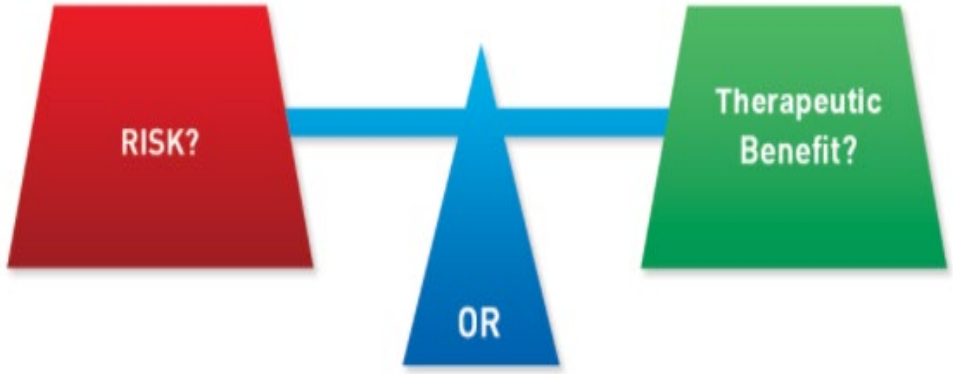
- Additional pharmacovigilance:
  - Non-clinical studies
  - Clinical trials
  - Post-authorisation safety studies

Risk minimisation activities

- Comprise a combination of routine and additional activities:
  - Routine: apply to every medicinal product
  - additional: only used when essential for the safe and effective use, need to justify its need, periodically reviewed.

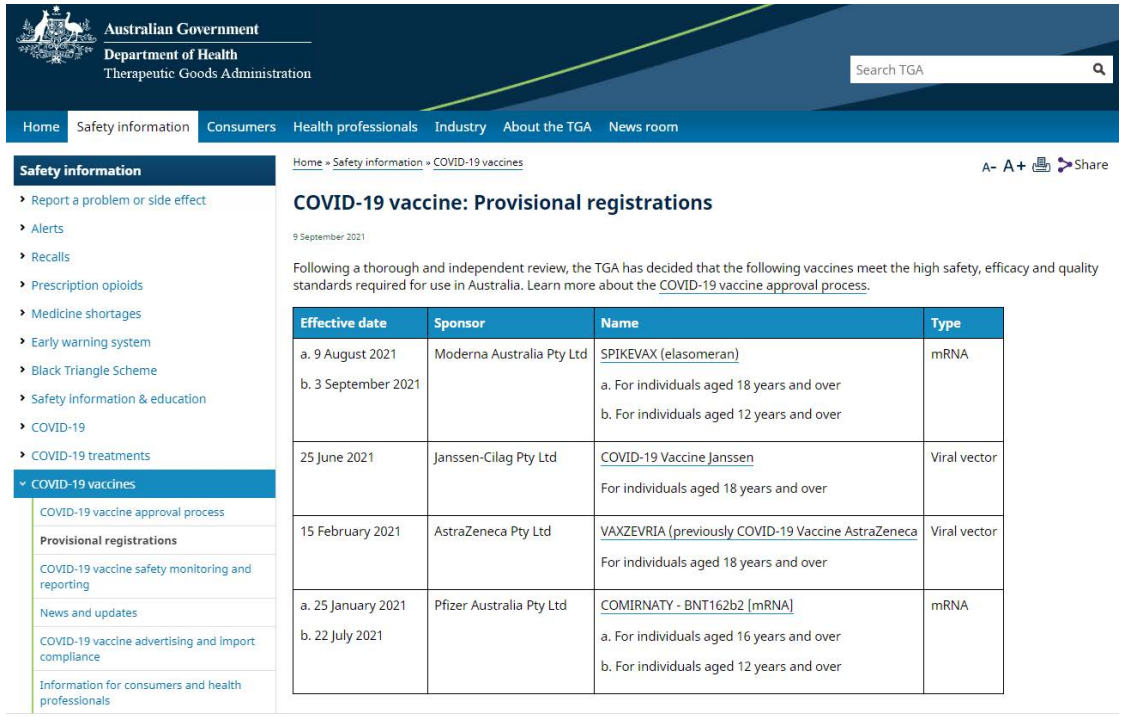
RMP evaluation

- Specific elements considered by the TGA RMP evaluation, such as:
  - Provisional registration status
  - Black Triangle Scheme
  - Products used to prevent/treat COVID-19



Provisional registration status

- Early access to new medicines: more evidence on safety is needed.
- Requirements:
  - Collection of confirmatory safety data
  - Enhanced post-market monitoring
  - Statements in PI and CMI
- Examples:
  - COVID-19 vaccines
  - Tisagenlecleucel, CAR-T therapy for B-cell acute lymphoblastic leukaemia



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Safety information

- Report a problem or side effect
- Alerts
- Recalls
- Prescription opioids
- Medicine shortages
- Early warning system
- Black Triangle Scheme
- Safety information & education
- COVID-19
- COVID-19 treatments
- COVID-19 vaccines
  - COVID-19 vaccine approval process
  - **Provisional registrations**
  - COVID-19 vaccine safety monitoring and reporting
  - News and updates
  - COVID-19 vaccine advertising and import compliance
  - Information for consumers and health professionals

Home » Safety information » COVID-19 vaccines

A- A+ Share

COVID-19 vaccine: Provisional registrations

9 September 2021

Following a thorough and independent review, the TGA has decided that the following vaccines meet the high safety, efficacy and quality standards required for use in Australia. Learn more about the COVID-19 vaccine approval process.

Effective date	Sponsor	Name	Type
a. 9 August 2021 b. 3 September 2021	Moderna Australia Pty Ltd	SPIKEVAX (elasomeran) a. For individuals aged 18 years and over b. For individuals aged 12 years and over	mRNA
25 June 2021	Janssen-Cilag Pty Ltd	COVID-19 Vaccine Janssen For individuals aged 18 years and over	Viral vector
15 February 2021	AstraZeneca Pty Ltd	VAXZEVRIA (previously COVID-19 Vaccine AstraZeneca For individuals aged 18 years and over	Viral vector
a. 25 January 2021 b. 22 July 2021	Pfizer Australia Pty Ltd	COMIRNATY - BNT162b2 [mRNA] a. For individuals aged 16 years and over b. For individuals aged 12 years and over	mRNA

Black triangle scheme

- Black triangle symbol, and accompanying text, on Product Information (PI) and Consumer Medicines Information (CMI)
- 5 years duration
- Which products are included?
  - Newly registered
  - Provisionally registered
  - Significantly different population, disease/condition

COVID-19 and its impact

Changes driven by clinical demand at the centre

RMPs – questions for you

- Do all medicines need same pharmacovigilance measures to monitor safety, why?
- Which is more important in developing a risk minimisation plan, safety evidence from the past, or how the product will be used in the future?
- If RMPs need to suit Australian context, what is the value of international collaboration, and how does this improve public health?

RMP resources

- *TGA Risk Management Plans Guidance with Australian-specific Annex template*

(https://www.tga.gov.au/publication/risk-management-plans-medicines-and-biologicals)

- *EMA Guideline on Good Pharmacovigilance Practices: Module V – Risk management systems (Rev 2)*

(https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf)

- *Collection of Confirmatory Data on Efficacy and Safety, Enhanced Monitoring Requirements for Products with Provisional Registration:*

(https://www.tga.gov.au/publication/provisional-registration-extension-and-transition-full-registration)

- *Black Triangle Scheme:*

(https://www.tga.gov.au/black-triangle-scheme)

- *EMA Guidance on Core Requirements for RMPs of COVID-19 Vaccines (https://www.ema.europa.eu/en/documents/other/consideration-core-requirements-rmps-covid-19-vaccines_en.pdf)*

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Post-market pharmacovigilance

- Why post-market pharmacovigilance?
- How the TGA does this?
- Adverse Event Management System
- Safety signals:
  - What is a safety signal?
  - Management of a safety signal
  - Potential responses to a signal
- Role of the sponsor
- Your role as a health professional

Why post-market pharmacovigilance?

Why post-market PV?

- **Identify new adverse events or change in rates of known reactions.**
  - not all adverse events are identified in pre-market clinical trials
  - small numbers of participants, so rare adverse events cannot be detected
    - “rule of 3” – 3N patients to detect adverse event with a frequency of 1/N
  - exclusion criteria → study population differs from population using medicine after registration
    - age, sex, pregnancy, comorbidities, concomitant medications
  - statistical aspects focus on efficacy endpoints not safety
  - experimental environment, tightly controlled vs ‘real world’
  - relatively short duration of trials, late adverse events not identified
- **Identify production and other quality issues.**

How the TGA does this?

- **Receiving AE reports and maintaining the Adverse Event Management System (AEMS) database**
  - selected information published in the searchable Database of Adverse Event Notifications (DAEN) on the TGA website.
- **Analysing adverse event reports and data regularly**
  - individual spontaneous reports for serious adverse events daily
  - some vaccines weekly (e.g. influenza during flu season)
  - Proportional Reporting Ratio (PRR) analysis for all medicines bimonthly.
- **Evaluating information from sponsors, literature, other drug regulatory authorities and WHO.**
- **Undertaking safety reviews/investigations and benefit-risk reviews.**
- **Safety issues tracked through a workflow database.**
- **Taking regulatory action* as needed**

PV in the times of COVID-19

- The TGA's ***COVID-19 vaccine safety monitoring plan*** aims at enhancing rapid detection, investigation and response to suspected adverse events following COVID immunisation.

https://www.tga.gov.au/resource/covid-19-vaccine-safety-monitoring-plan

- Key **strategies** of the plan include:

- timely collection and management of reports of COVID-19 vaccine adverse events following immunisation
- timely detection and investigation of COVID-19 vaccine safety signals
- timely action to address any COVID-19 vaccine safety concerns
- timely communications to inform the public of emerging COVID-19 vaccine safety information and to support public confidence in vaccines
- close collaboration and coordination of effort with other vaccine safety stakeholder groups.

- Rapid and appropriate management of COVID vaccine related safety issues is crucial to maintaining public confidence in the immunisation program.

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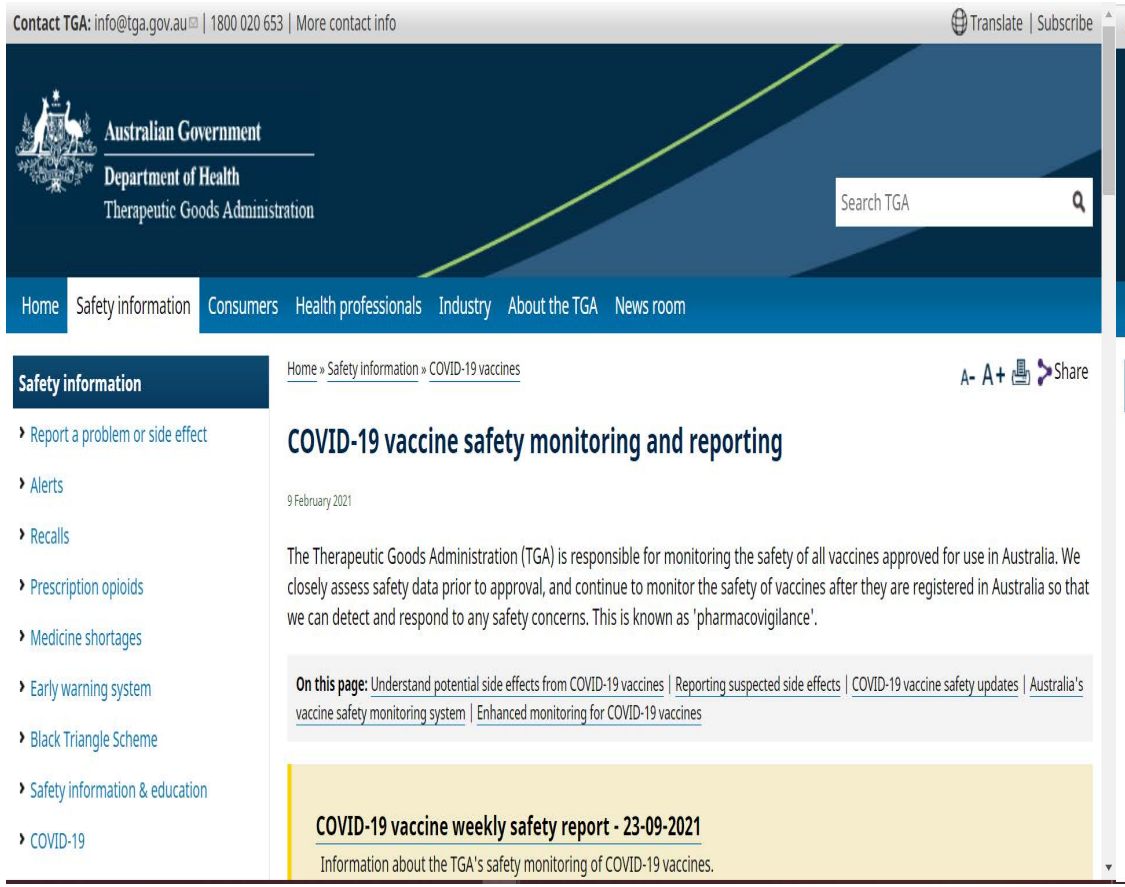
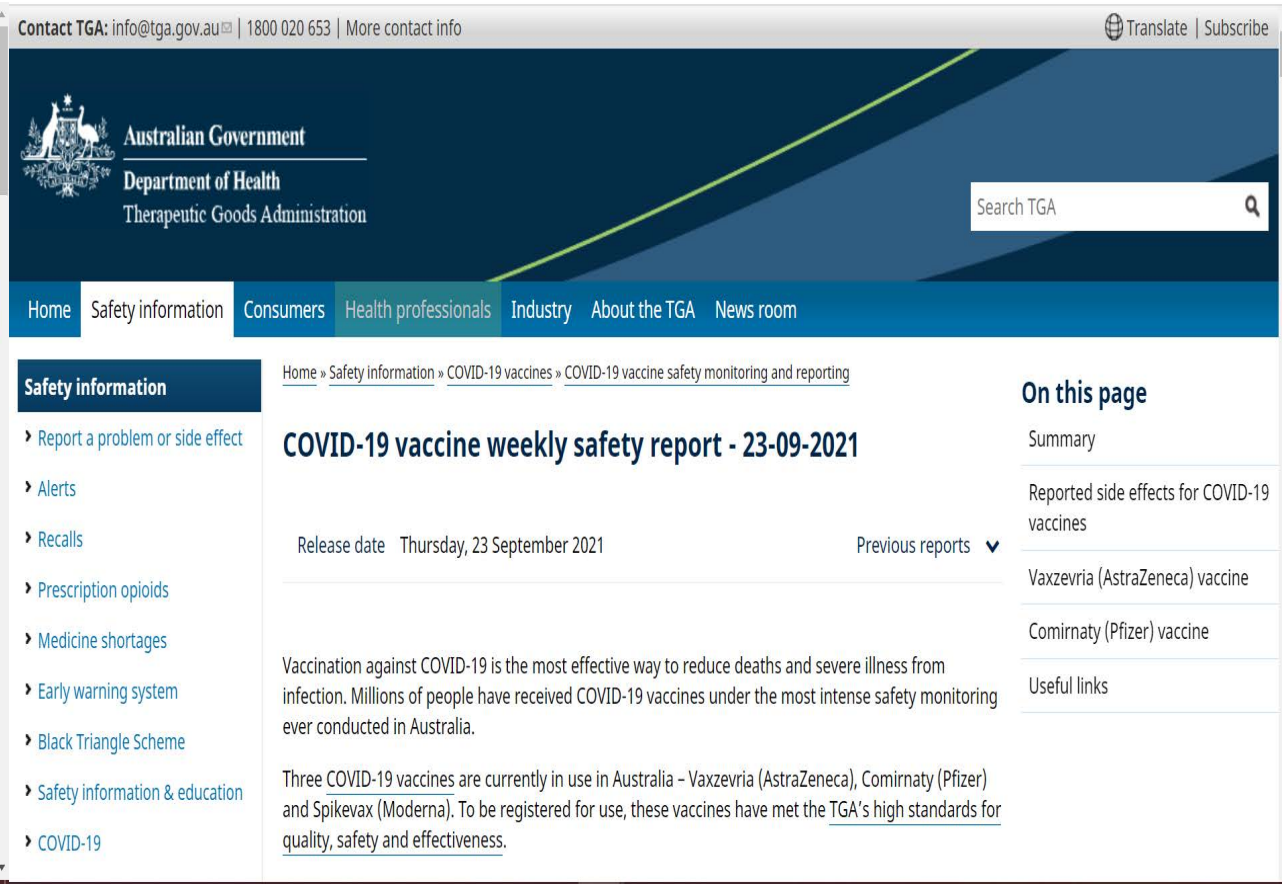
PV in the times of COVID-19





Adverse Event Management System (AEMS)

- Adverse event data collection began August 1964 (post thalidomide)
  - data collection and storage initially paper based; electronic since 1971.
- Spontaneous reporting system
  - **mandatory** for sponsors (within 15 calendar days for serious adverse reactions)
  - **voluntary** for health professionals, consumers
  - vaccine reports from State and Territory Health Departments
  - Benefits: all drugs, all patients, fast and relatively cheap
  - Drawbacks: under-reporting, lack of key information, no denominator.
- As of September 2021, there were:
  - 564,053 individual case safety reports in the database
  - ~23% are vaccine reports.

Important definitions

- **Adverse event (AE)**
  - Any untoward medical occurrence temporally associated with the use of a medicine, but not necessarily causally related

- **Adverse drug reaction (ADR)**
  - A noxious or unintended response to a medicine
  - Distinguished from an AE by the fact that a causal association with a medicine is suspected

- ***Serious* ADR/AE**
  - Any ADR/AE that results in death, is life-threatening, requires hospitalisation or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital abnormality, is considered medically important

Who reports adverse events?

- Information on suspected adverse events/adverse drug reactions is submitted as individual case reports by:
  - sponsors (mandated – serious adverse events within 15 days)
  - health professionals (e.g. doctors, pharmacists, others)
  - hospitals
  - consumers
  - State and Territory immunisation coordinators (vaccines).

How reports are received

- Online reporting via TGA website – sponsors, consumers and health professionals
  - On line AEMS portal ; Via GuildLink
- Letters/emails/telephone – health professionals and consumers.
- Council for International Organizations of Medical Sciences (CIOMS) form (international format) – sponsors.
- Blue card - health professionals and consumers.
- Telephone via NPS MedicineWise Adverse Medicine Event Line – consumers.
- Vaccines – State/Territory Health Departments or agencies (e.g. SAEFVic)
  - various formats.

AEMS function

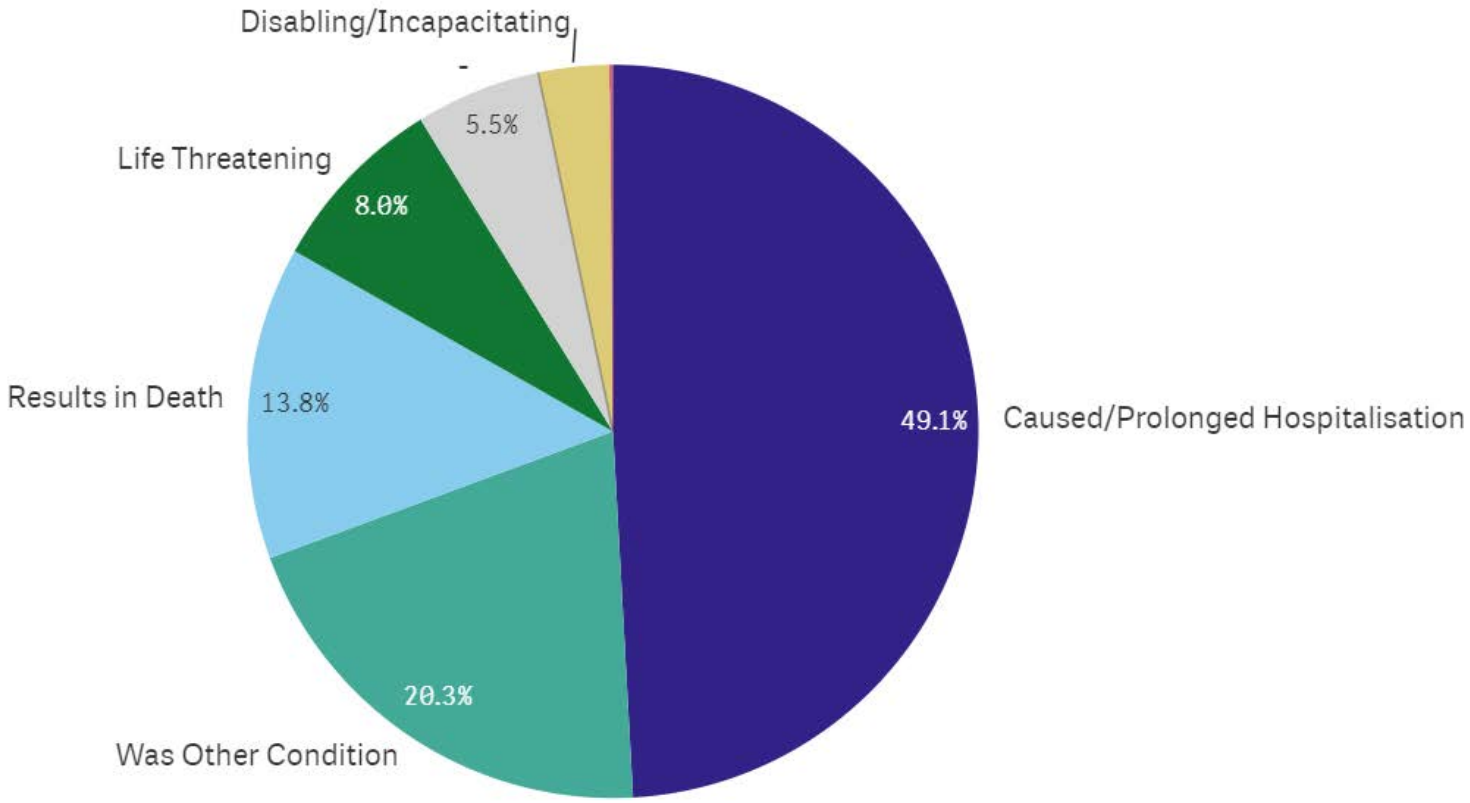
- Regardless of the input channel, data are triaged and entered in to AEMS with the analyses of seriousness and causality.
- Reactions are coded using MedDRA terminology, while drugs are coded using an in-house classification based on the Anatomical Therapeutic Chemical (ATC) codes.
- Follow-up information may be sought in order to gain information essential for determining causality, such as concomitant medication, medical history, concurrent illness, time to onset of adverse event confounders, etc.
- Follow-up information is sought from reporter:
  - if adverse event is serious, unexpected, or the reaction or the drug is of special interest, further information will be requested up to three times
  - standard questionnaires based on Brighton Collaboration definitions for some AEFIs.

Serious reports

- ~30% of reports we receive are classified as ‘Serious’
  - Hospitalised or hospitalisation period extended
  - Attended emergency department or specialist
  - Life threatening
  - Death
  - recovery with sequelae - incapacity/disability
  - Congenital anomaly.

- Sponsors **must** report serious adverse events to us within 15 calendar days

Seriousness (current data)



Causality assessment

- Based on WHO classification:
  - Certain
  - Probable
  - Possible
  - Unclear

DAEN

- **D**atabase of **A**dverse **E**vent **N**otifications
- Publically available, searchable database on the TGA website http://www.tga.gov.au/database-adverse-event-notifications-daen

- Caveats include:
  - The reports received by the TGA contain suspected associations that reflect the observations of an individual reporter
  - There might be no causal relationship between the adverse event and the medicine
  - The search results cannot be used to determine the incidence of an adverse event.
  - Despite regular checking, it is possible that the database contains some duplicate reports, as a single case can be reported by multiple sources, and this is not always easy to identify.

What is a safety signal?

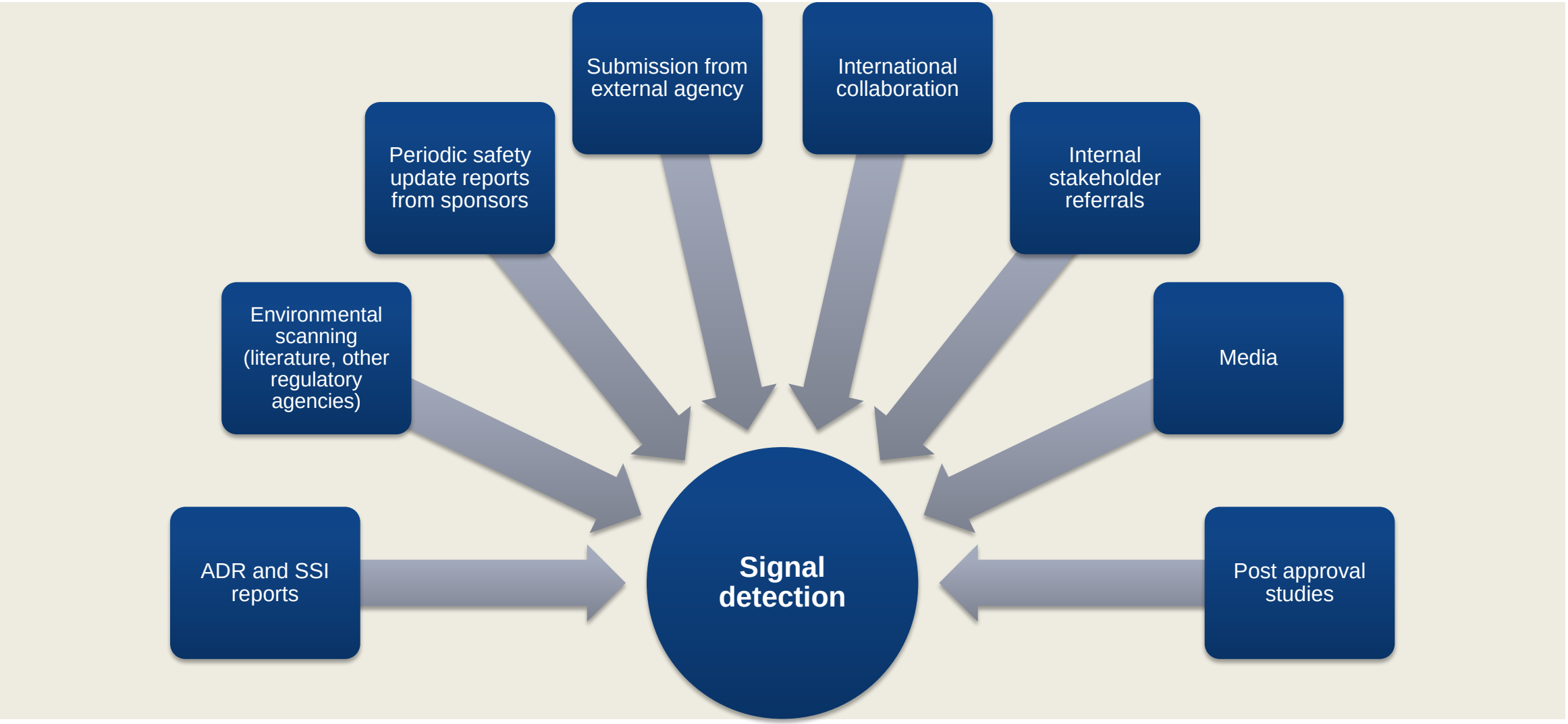
"Information that arises from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be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

Hauben and Aronson, *Drug Safety* 2009,32(2):99-110

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously"

(WHO definition)

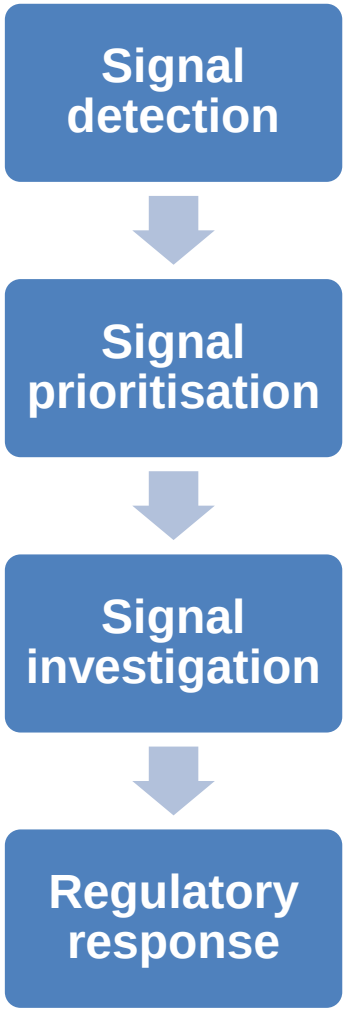
Sources of Safety Signal



Management of safety signals

- A safety signal is a possible safety issue that needs further investigation.
- Three aspects:
  - signal **detection**/identification
  - signal **investigation**/assessment
  - signal **response**.
- Signal investigation is undertaken to determine whether:
  - the signal can be ‘verified’ → appropriate response determined
  - the signal can be ‘refuted’ → a false positive with no need for further action
  - the signal remains ‘indeterminate’ → more data/further observation is needed.

Management of safety signals



Signal detection/identification

- A mix of proactive and reactive activities to identify harmful effects of medicines:
  - review of spontaneous ADR reports
    - includes use of data mining tool(s) such as the PRR – bimonthly
  - review of Periodic Safety Update Reports(PSUR) and other safety summary reports submitted by sponsors
  - review of international vigilance activities and reports
  - review of published literature
  - review of post approval studies.
  - review of pharmacoepidemiology studies in other relevant data sets, such as PBS and linked health data sets.

Signal investigation/assessment

- Assess the nature, magnitude and health significance of safety signals and their impact on the overall benefit-risk of the product
  - apply analytical skills in pharmacovigilance, epidemiology, biostatistics, risk assessment and clinical practice
  - use expert analysis and advice
    - Advisory Committee on Medicines (ACM)
    - Advisory Committee on Vaccines (ACV)
    - convene Expert Panels for some issues
  - use international data and liaise with other regulators.

Potential responses to a signal

- Signal **response** – action taken to mitigate the risk(s):
  - alteration of product documents
    - Product information (PI) and Consumer Medicine Information (CMI)
      - indications, contraindications, warnings, dosage and administration, boxed warnings
  - packaging and labelling changes
  - other changes to conditions of registration
    - role of the RMP
  - communication of important safety and benefit-risk information
    - Sponsor – DHCP letters
    - TGA – web statements, Medicine Safety Update (MSU) articles
    - TGA liaison with NPS MedicineWise, professional colleges.
  - product removal, i.e. suspension, cancellation, recall

Example – lumiracoxib cancellation

- Lumiracoxib:
  - registered July 2004
  - COX-2 inhibitor, not the first in class
  - PBS subsidy August 2006
  - 60,000 users.
- Eight reports of serious hepatotoxicity, with two deaths and two transplants.
- Registration cancelled August 2007.
- Liver death (fatality or transplant) 1 in 15,000:
  - rule of 3: would need 45,000 in a trial
  - therefore, impossible to detect premarket
  - but a significant risk considering underlying disease, efficacy and availability of alternatives.

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Lumiracoxib (Prexige): Urgent advice regarding management of patients

Safety alert

13 August 2007

- **ALL patients should stop taking Lumiracoxib immediately.**
- **ALL patients should be assessed by their doctor for any clinical or biochemical evidence of liver damage.**

Lumiracoxib (tradename Prexige) was approved for the indications:

- *Symptomatic relief in the treatment of osteoarthritis.*
- *Relief of acute pain, including post-operative pain and pain related to dental procedures.*
- *Relief of pain due to primary dysmenorrhoea.*

Related information

- Medicines regulator cancels registration of anti inflammatory drug, Lumiracoxib (Prexige) media statement, 11 August 2007
- Recall notice: Lumiracoxib (Prexige) 10 August 2007

PSUR Review

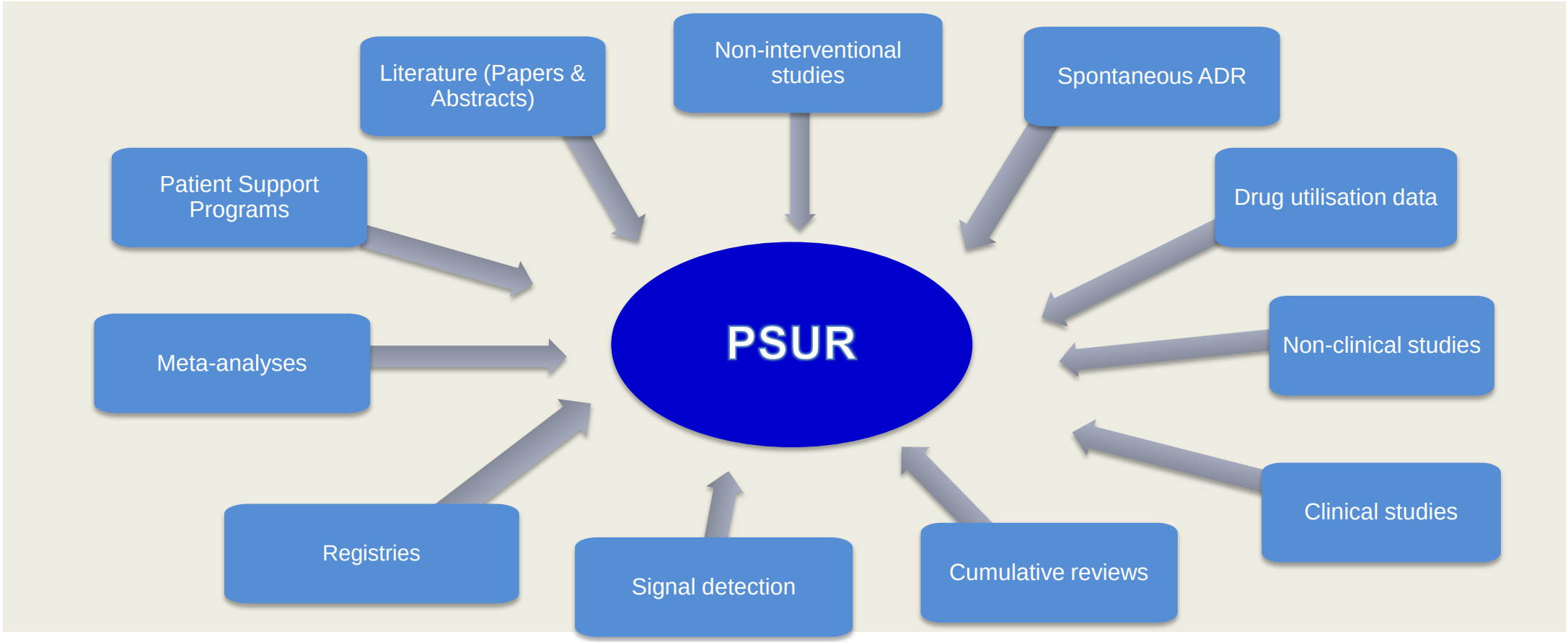
What is a PSUR?

Periodic safety update report (PSUR) is:

- A pharmacovigilance document intended to provide a systematic review of global safety data and a critical analysis of benefit/risk balance at defined points in time in the lifecycle of an approved medicinal product.
- It aims to analyse balance of benefits and risks, by taking into account new information in the context of cumulative data.
- Prepared by Sponsors and submitted to the TGA at intervals which are currently defined under the ‘Conditions of Registration’.

Place of PSUR in Pharmacovigilance

PSUR is not a replacement for other safety monitoring!



PSUR Review at the TGA

- The PSUR review process is an integral part of the TGA's Enhanced Vigilance Framework.
- This process assesses the benefit/risk balance of marketed drugs at pre-defined intervals.
- PSUR review intends to provide the necessary safety counterbalance, especially to early registrations of high priority medicinal products which have a nascent safety profile at the time of approval.
- PSURs are not required for all registered medicines. A risk-based approach is used to determine the requirement, frequency and duration of PSUR submission

PSUR Review outcomes: *Recommendations for*

Maintenance
No further evaluation/action recommended

Variations
-PI/RMP updates recommended.

Signal Evaluation
-Recommendations for further signal/safety update evaluation.

Additional PV activities (to Sponsor)
- to perform safety studies/safety reviews.
-to monitor & report on additional safety topics.

Role of the sponsor

- *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements* includes mandatory adverse event reporting for sponsors and guidance on pharmacovigilance systems.
  - https://www.tga.gov.au/publication/pharmacovigilance-responsibilities-medicine-sponsors

- *International scientific guidelines adopted in Australia*
  www.tga.gov.au/pharmacovigilance-guidelines

Sponsor reporting requirements

Report type	How to report	Regulatory Reporting timeframe
Contact person for pharmacovigilance	Via the TGA Business Services (TBS) system by the sponsor administrator	≤ 15 calendar days
Significant safety issues	In writing to the PSAB Signal Investigation Coordinator, preferably via email to si.coordinator@health.gov.au	≤ 72 hours
Serious adverse reaction reports that occurred in Australia	Blue card/CIOMS form/E2B reports/online reporting form Email: adr.reports@health.gov.au or e2b.reports@tga.gov.au (ICH E2B formatted reports only)	≤ 15 calendar days
Quality defects, adulterated products, counterfeit products	For significant safety issues, email: si.coordinator@health.gov.au For serious adverse reactions, email: adr.reports@health.gov.au For quality defects that may warrant a recall, email: recalls@health.gov.au	In accordance with the timeframe for serious adverse reactions or a significant safety issue as applicable
Non-serious adverse reaction reports and overseas adverse reaction reports	Presented as a cumulative table in a Periodic Safety Update Report (PSUR) where required, or in the format requested by the TGA	As specified by the TGA PSUR reporting requirements or specific request

Your role as a health professional

- You play an important role in monitoring the safety of medicines by reporting any suspected adverse events to the TGA.
- The TGA is particularly interested in:
  - suspected reactions involving new medicines
  - serious or unexpected reactions to medicines
  - serious medicine interactions.
- You don’t need to be certain to report, just suspicious!
- Reports can be made online, or by phone, fax or email.
- Visit the TGA website for more information about reporting (https://www.tga.gov.au/reporting-adverse-events)

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