Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance - a regulator's perspective

Vicky Dong
Shabnam Sharan
Pharmacovigilance and Special Access Branch
Medicines Regulation Division

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TGA Health Safety Regulation

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Overview

- Who we are and what we do
  - Pharmacovigilance and Special Access Branch
- What is pharmacovigilance?
- Premarket pharmacovigilance
  - Risk Management Plans
- Post-market pharmacovigilance
  - Adverse event reporting
  - Signal detection and investigation
  - Pharmacovigilance inspection

Who we are and what we do

- TGA is part of the Commonwealth Department of Health.
- TGA was established in 1990 to ‘safeguard and enhance the health of the Australian community through effective and timely regulation of therapeutic goods’.
- We provide a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods used in, or exported from, Australia.
- We apply scientific and clinical expertise to decision making.

What we do (continued)

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

Pharmacovigilance and Special Access Branch (PSAB)

- Responsible for post-market (and some pre-market) monitoring and compliance of medicines on the Australian Register of Therapeutic Goods (ARTG).
- Includes:
  - monitoring of more than 27,354 medicines (13,000+ registered)
  - each year the branch administers/undertakes:
    - More than 21,000 adverse event reports relating to medicines/vaccines
    - about 130 Risk Management Plan evaluations
    - numerous safety reviews of medicines and vaccines
    - 60,000 notifications (Clinical Trials, Authorised Prescriber, Special Access Scheme) managed by the Experimental Products Section.

What is pharmacovigilance?

- The World Health Organization (WHO) describes pharmacovigilance as *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem*. This includes:
  - collection and evaluation of spontaneous case reports of suspected adverse events
  - pharmacoepidemiology studies (ICH 2004).

Premarket pharmacovigilance

- Risk Management Plans (RMPs)
  - What is in an RMP?
  - When is an RMP required?
  - Considering the Australian context
  - RMP components
  - RMP evaluation
  - Lifecycle of an RMP
  - RMP resources
  - RMPs in practice

Risk Management Plans (RMPs)

- An RMP is a detailed description of a risk management system.
- RMPs contain:
  - a description and analysis of the safety profile of the medicine
  - a set of pharmacovigilance and risk minimisation activities.
- Covers the entire **life cycle** of the medicine.

What is in an RMP?

- An RMP must include:
  - what is known about the medicine's safety profile
  - consideration for what is **not** known about the safety of the product
  - a summary of key safety concerns.
- RMP components:
  - Safety Specification
  - Summary of Safety Concerns
  - Pharmacovigilance Plan
  - Risk Minimisation Plan

When is an RMP required?

- An RMP must accompany all applications for:
  - new chemical/biological entities
  - vaccines
  - Class 3 and 4 biological products
  - previously registered medicines where there is a **significant** change to registration status (e.g. different target population, new disease, extension into paediatric use, new dosage form).

Considering the Australian context

- Things to consider about risk management of medicines in Australia include:
  - Indigenous population
  - large Asian population
  - rurality/lack of specialist services
  - differences between state and federal control over some aspects of how medicines are used (e.g. scheduling and extemporaneous compounding)
  - risk management activities proposed for other jurisdictions may require adaption to Australian systems.

Pharmacovigilance plan

- Pharmacovigilance objectives:
  - monitor the occurrence of known risks post-approval
  - identify new and unknown risks that were not apparent in clinical development
  - gain an understanding of ‘real world use’ vs clinical study use
  - further inform and characterise the safety profile of the medicine.

Pharmacovigilance plan (continued)

- Can comprise a combination of routine and additional activities.
- Routine pharmacovigilance must include:
  - collection, follow-up and reporting of spontaneous adverse events
  - analysis of data and reporting in Periodic Safety Update Reports (PSURs).
- Sponsors have obligations for all medicines registered in Australia.
- Black triangle scheme to enhance monitoring

Black triangle scheme

- Purpose: to identify new prescription medicines, or those used in significantly different ways for adverse event reporting.
- Effect: black triangle symbol, and accompanying text, will appear on Product Information (PI) and Consumer Medicines Information (CMI) of products included in the scheme for five years
- Which products are included:
  - Newly registered
  - Provisionally registered
  - Significantly different population, disease/condition

Risk minimisation activities

- Risk minimisation objectives:
  - ensure risks are minimised by:
    - including warnings/precautions/contraindications on product information/packaging
    - educating patients and health professionals of specific risks
    - restricting access to a particular prescriber/patient group
    - encouraging reporting of adverse events.

- Can comprise a combination of routine and additional activities:
  - routine:
    - Product Information
    - Consumer Medicine Information
    - Directions for Use document
    - labelling, pack size and design
    - legal (prescription) status.
  - additional:
    - education programs
    - prescriber checklists
    - DHCP letters
    - controlled access programs
    - medical software alerts.

RMP evaluation

- RMPs are evaluated as part of the registration application.
- Each RMP is considered on a case-by-case basis (no one-size-fits-all).
- Evaluator makes recommendations to the ‘Delegate’, who considers these and recommendations from other evaluation areas (e.g. clinical, toxicology, pharmaceutical chemistry) in deciding to approve or reject the application.
- The sponsor has an opportunity before the decision to respond to issues raised during the TGA evaluation process.
- The TGA can seek advice regarding any aspect of the submission through a number of advisory committees.
- Multidisciplinary evaluation team.

Lifecycle of an RMP

- An RMP is a *living* document.
- All sponsors must periodically review and amend the RMP as new information about the medicine becomes available.
- Updating the RMP is not a surrogate for notifying the TGA of a change in the benefit-risk of the product or of a particular safety issue that comes to light.
- Post-registration safety data is reported to the TGA through mandated adverse event and significant safety issue reporting, as well as via PSURs.

RMP resources

- *TGA Risk Management Plans Guidance*

(https://www.tga.gov.au/book/export/html/4188)

- *TGA Australian-specific Annex Template*

(https://www.tga.gov.au/book-page/australian-specific-annex-template)

- *EMA Guideline on good pharmacovigilance practices: Module V – Risk management systems*

(www.tga.gov.au/pharmacovigilance-guidelines)

- *Pharmacovigilance responsibilities of medicines sponsors: Australian recommendations and requirements*

(https://www.tga.gov.au/publication/pharmacovigilance-responsibilities-medicine-sponsors *)*

- *Black triangle shceme: information for sponsors*

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

- CIOMS IX *Practical Approaches to Risk Minimisation for Medicinal Products*

RMPs in practice – a hypothetical

- Imagimist is a new nasal spray shown in clinical trials to be effective for the treatment of panic attacks. It has not been approved elsewhere and therefore no post-marketing data is available.
- Proposed dose is 1 x 10 microgram spray in each nostril at first symptoms of a panic attack (maximum 2 doses/day).
- Clinical safety issues:
  - local reactions (including epistaxis)
  - headache
  - possible toxicity in large doses
  - increased QT interval in patients taking SSRIs.
- Toxicology safety issues:
  - in a rabbit model there has been a suggestion of nasal tumours at the site of application which have not been seen in human trials.

Questions to ask (assuming a positive benefit-risk balance)

- What is the target population? What is the clinical need? Is there likely to be widespread use?
- From a public health perspective what are the key risks?
- What is the global perspective?
- Do these risks require additional pharmacovigilance? Why?
- Does the potential for off-label use/medication error need to be managed?
- What warnings/precautions should be included in the Product Information?
- Are product warnings sufficient ? Why?

Workshop activity

- Pharmacovigilance activities
  - clinical trials
  - post-authorisation safety studies
  - drug utilisation studies
  - patient registries
  - physician surveys
  - prescription event monitoring
  - Black triangle scheme

- Risk minimisation activities
  - Product information/labelling
  - education programs
  - prescriber checklists
  - DHCP letters
  - controlled access programs
  - medical software alerts.

RMPs – take home messages

- There is no one size fits all approach to risk management.
- Risk management should be product/disease/target population specific.
- Risk minimisation technologies (e.g. prescriber software alerts) are becoming increasingly available – think outside the box!
- Australian context – what works for another jurisdiction may not work here.
- **Public health and safety is the key priority.**

Questions

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Post-market pharmacovigilance

- Why post-market pharmacovigilance?
- TGA post-market pharmacovigilance activities
- Adverse Drug Reaction System
- What is a safety signal?
- Management of safety signals
- Potential responses to a signal
- Role of the sponsor
- Your role as a health professional

Why post-market pharmacovigilance?

- **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 à 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…

- 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 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 regulators and WHO.
- Undertaking safety filters, safety reviews and risk benefit reviews.
- Communicating information to health professionals and consumers.
- Taking regulatory action as needed.
- Issues tracked through a workflow database.

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

Adverse event management system

- 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 days for serious reactions)
  - voluntary for health professionals, consumers
  - vaccine reports from State and Territory Health Departments
  - benefits are all drugs, all patients, fast and relatively cheap
  - drawbacks are under-reporting, lack of key information, no denominator.
- At 13 July 2017, there were:
  - 414,544 individual case safety reports in the database
  - ~12% are vaccine reports.
- Currently the WHO global database (Vigibase) holds over 17.5 million reports.

AEMS

- In 2018 the Adverse Events Monitoring system (AEMS) database replaced the former ADRS (Adverse Drug Reaction System) database.
- AEMS supports electronic data interchange (EDI) which makes it possible for sponsors to directly put AE reports into the database.
- Health professionals and consumers can also report adverse events using an on-line form on the AEMS web portal. The portal transfers data entered into the form directly into the AEMS database.
- Two distinct reporting forms: one for sponsors and one for health professionals/consumers.

Volume of reports

- In 2017, the TGA received 21,359 adverse event reports.
- ~8% were assessed as being ‘causality unclear’
  - not an adverse event
  - insufficient information to assess
  - reaction was not associated or extremely unlikely to be associated with the medicine
  - duplicate reports
  - these reports were ‘general listed’
    - available for review/updating but not routinely analysed
    - not included in the DAEN on the TGA website.

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

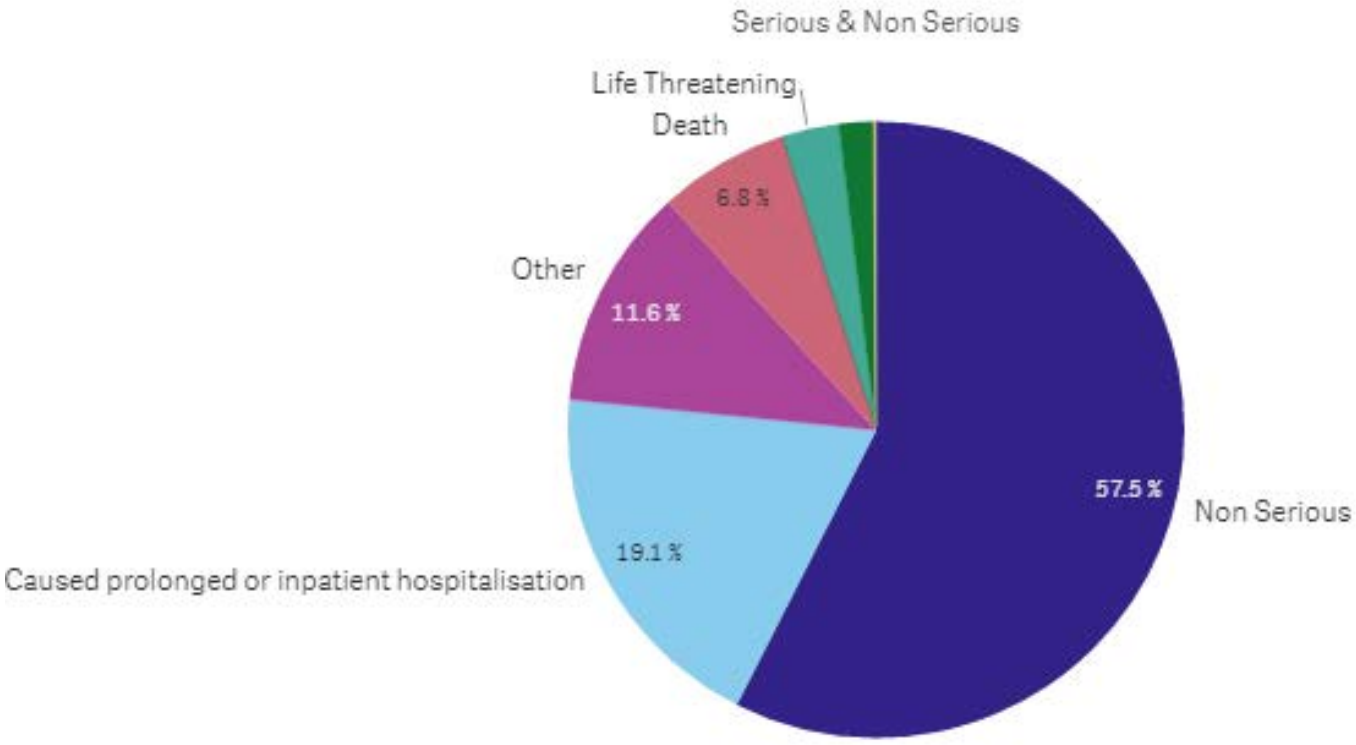
- Caveats include:
  - The reports received by the TGA contain suspected associations that reflect the observations of an individual reporter
  - There might be no relationship between the adverse event and the medicine
  - The search results cannot be used to determine the incidence of an adverse event.
  - 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.

Serious reports

- ~40% 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 days

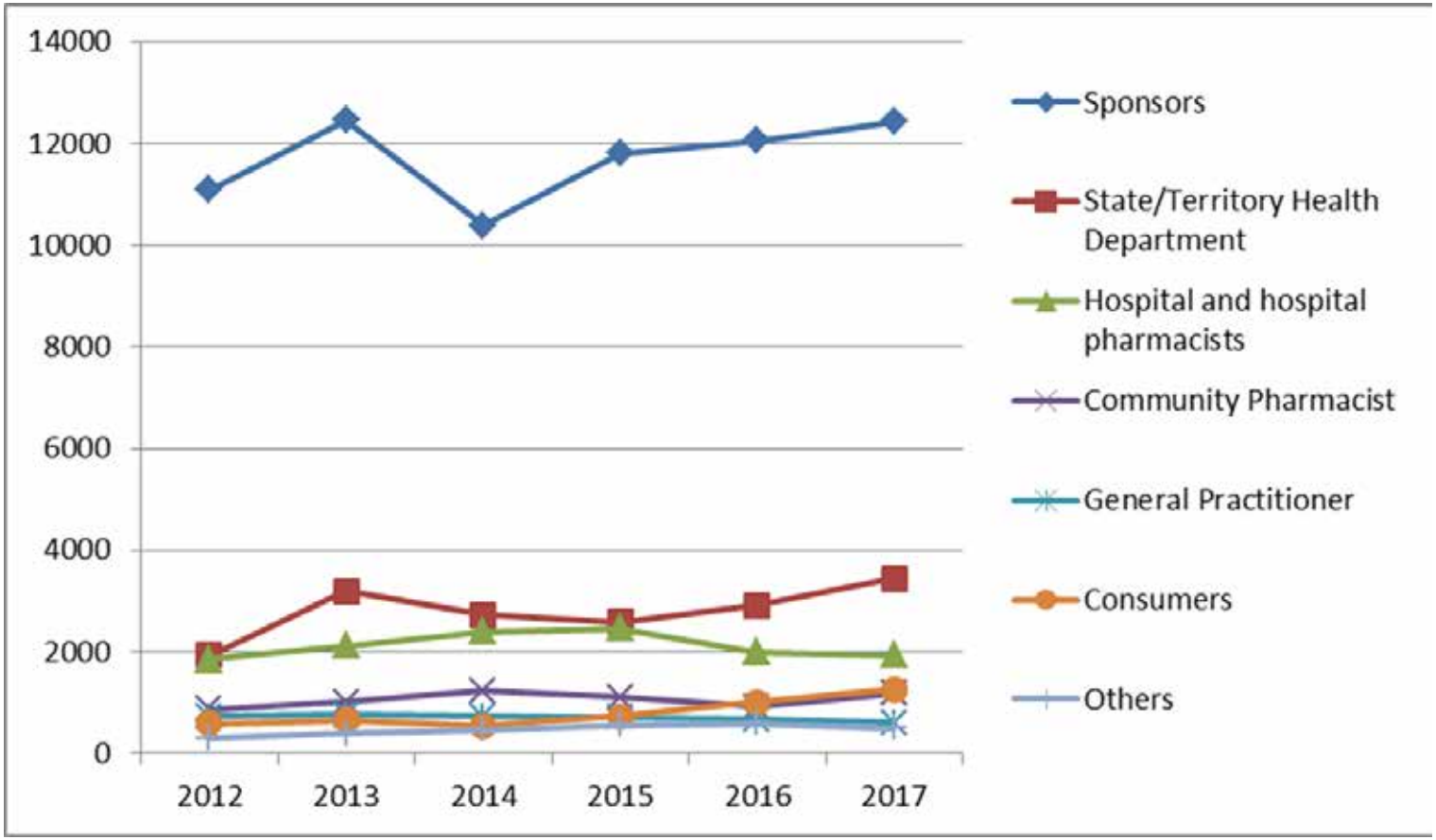
Seriousness (current data)



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).

Volume of adverse event reports received by the TGA (2012-2017)



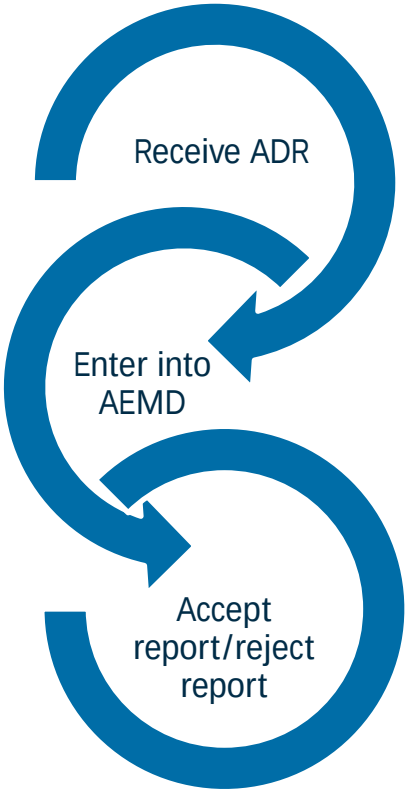
How reports are received

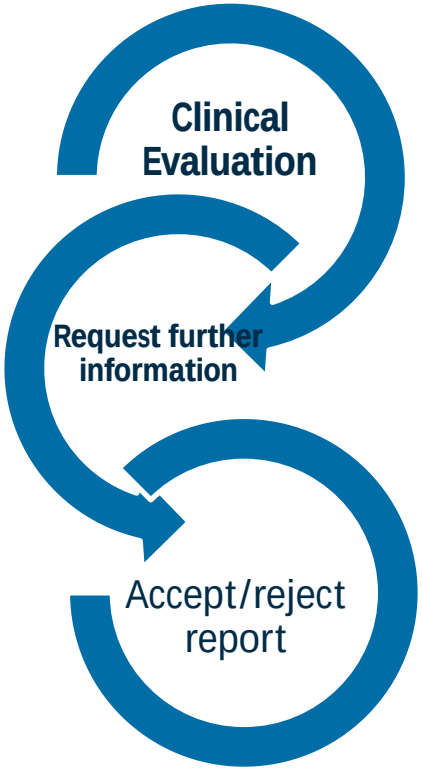
- Blue card - health professionals and consumers.
- Council for International Organizations of Medical Sciences (CIOMS) form (international format) – sponsors.
- Letters/emails/telephone – health professionals and consumers.
- Online reporting via TGA website – sponsors, consumers and health professionals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

Entry into database

- Regardless of the input channel, data are entered by staff in the data entry team who:
  - triage reports and enter reports in to AEMS:
    - database staff – non-serious events e.g. nausea, injection-site reactions, or
    - clinical evaluators – serious adverse events or complex reports
  - attach supporting documents
  - generate acknowledgement letters.
- Reactions are coded using MedDRA terminology, while drugs are coded using an in-house classification based on the Anatomical Therapeutic Chemical (ATC) codes.
- If multiple adverse events are reported, each is individually coded.
- Coding conventions, e.g. liver injury requires specific information on LFT test results before the coding term can be used.

Data entry and Clinical Evaluation





Follow-up information

- Need sufficient detail to determine causality.
- Require information on concomitant medication, medical history, concurrent illness, time to onset of adverse event.
- Need to identify confounders and determine temporal association.
- Seek further information (follow-up) 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.

Causality assessment

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

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

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’ à appropriate response determined
  - the signal can be ‘refuted’ à a false positive with no need for further action
  - the signal remains ‘indeterminate’ à more data/further observation is needed.

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 PSURs and other data from 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.

Investigation/assessment (continued)

- Initial **investigation**:
  - generally short evaluation of the issue
  - standard template
  - findings presented to the team
  - makes recommendations for further action (if needed).
- May be followed up with full safety review and/or risk benefit review.
- The TGA may seek additional information or comment from sponsors during the initial or follow-up stages of investigation.
- May result in commission of pharmacoepidemiological study (e.g. rotavirus and intussusception).
- Informs the signal response.

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.

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/sites/default/files/pharmacovigilance-responsibilities-medicine-sponsors.pdf
  - www.tga.gov.au/pharmacovigilance-guidelines (for other resources).

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)

Workshop activity

Further information

- The TGA publishes a wide variety of information relating to medicines.
- For example:
  - Australian Register of Therapeutic Goods
  - **Product recalls**
  - **Alerts**
  - Monitoring communications
  - Medicine shortages initiative
  - **Product Information/Consumer Medicine Information**
  - Database of Adverse Event Notifications
  - Medicine Safety Update.

Questions