Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance

A regulator's perspective

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UTS Molecule to market course

TGA Health Safety Regulation

19 October 2016

Overview

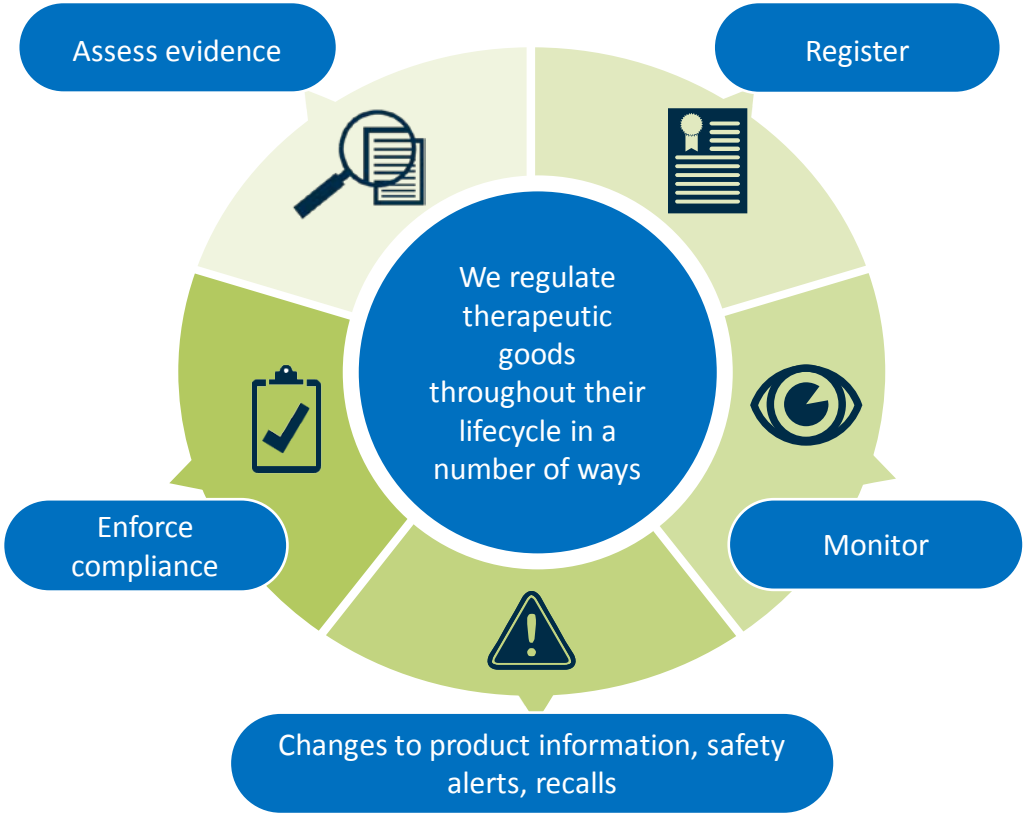
- What is pharmacovigilance?
- Who we are and what we do
  - Pharmacovigilance and Special Access Branch
- Premarket pharmacovigilance
  - Risk Management Plans
- Post-market pharmacovigilance
  - Adverse event reporting
  - Signal detection and investigation

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'.
- Provides a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods used in, or exported from, Australia.
- Applies 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:
  - premarket
  - post-market.



Pharmacovigilance and Special Access Branch

- Responsible for post-market (and some premarket) monitoring and compliance of medicines on the Australian Register of Therapeutic Goods (ARTG).
- Including:
  - monitoring of more than 27,354 medicines (13,000+ registered)
  - each year the branch administers/undertakes:
    - about 18,000 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?

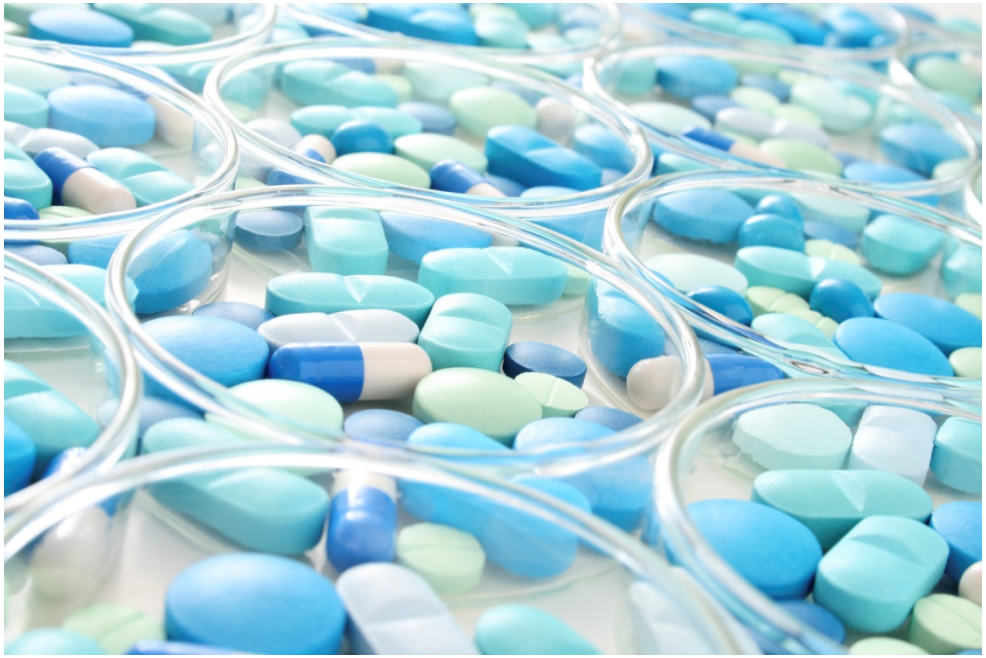
- The World Health Organization (WHO) describes pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. This includes:
  - collection and evaluation of spontaneous case reports of suspected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

When is an RMP required?

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

Considering the Australian context

- Registering a medicine in the European Union also requires an RMP.
- The TGA accepts EU RMPs for assessment, but some parts may not be relatable to 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 registered medicines, even if not marketed in Australia.
- Additional pharmacovigilance can include:
  - clinical trials
  - post-authorisation safety studies
  - drug utilisation studies
  - patient registries
  - physician surveys
  - prescription event monitoring.

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. RMPs are referred to the Advisory Committee on the Safety of Medicines.
- Current evaluation team comprises doctors, pharmacists and a toxicologist.

Lifecycle of an RMP

- Typically, the TGA assesses an RMP early in the medicine's lifecycle.
- Although imposed as a condition of registration, the TGA acknowledges an RMP is a living document.
- All sponsors must periodically review and amend the RMP as further 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*

(www.tga.gov.au/publication/risk-management-plans)

- *TGA Australian-specific Annex Template*

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

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

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

- *Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines*

(www.tga.gov.au/australian-requirements-and-recommendations-pharmacovigilance-responsibilities-sponsors-medicines)

- 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 neoplastic lesions 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

- 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!
- Australia is different – what works for another jurisdiction may not work here.
- **Public health and safety is the key priority.**

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 → 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 Drug Reaction System (ADRS) 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)
  - Proportional Reporting Ratio (PRR) 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.

Adverse Drug Reaction 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 20 August 2015, there were:
  - 328,664 individual case reports in the database
  - of which over 306,330 used for routine analysis
  - 37914 of these (12%) were vaccines.
- In 2014, WHO global database (Vigibase) held over 9 million reports.

Volume of reports

- In 2014, the TGA received over 18,000 adverse event reports.
- Around 1800 (~10%) 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
    - these reports were ‘general listed’
    - available for review/updating but not routinely analysed
    - not 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 https://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.

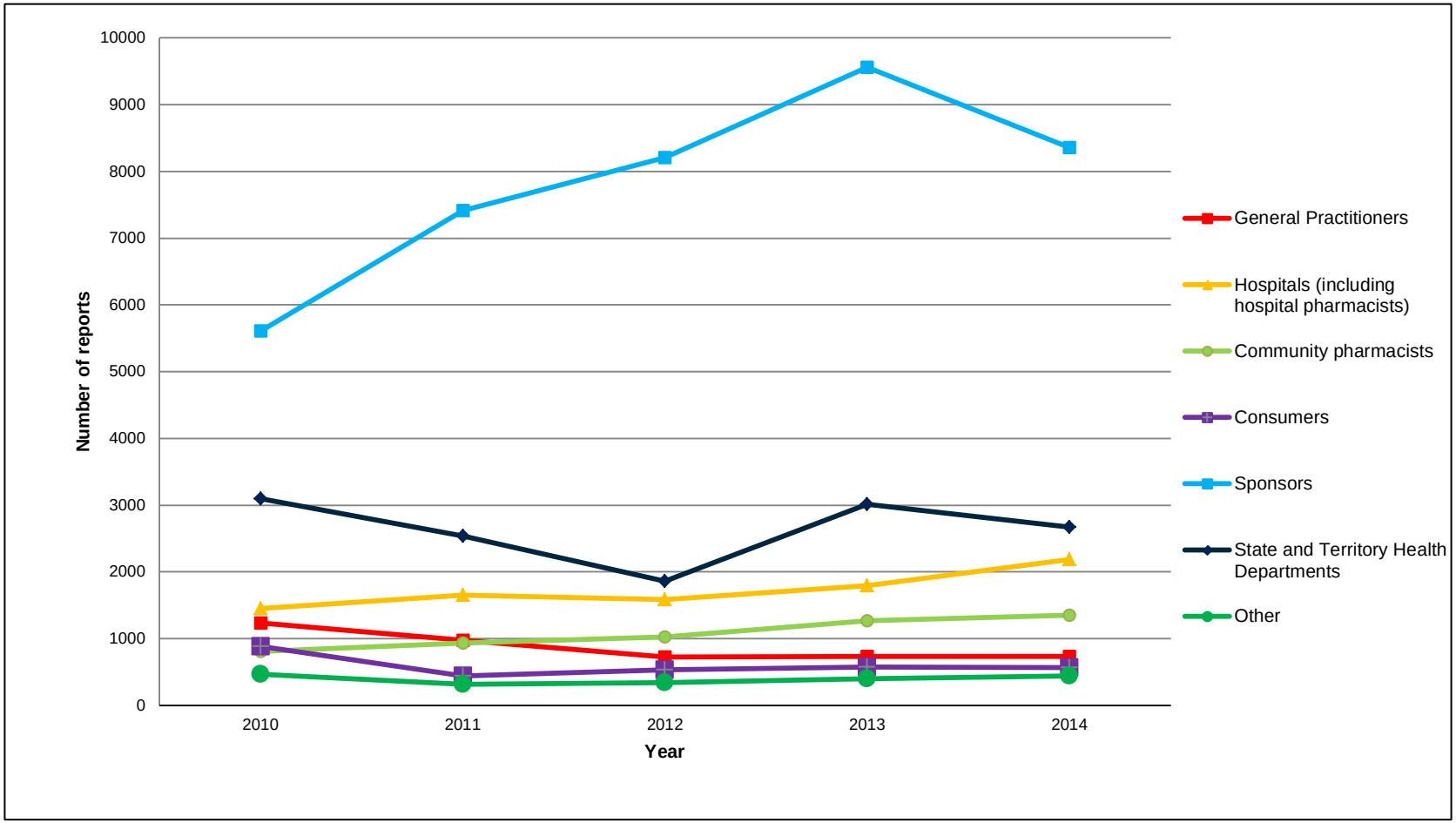
Serious reports

- 30% of reports were classified as ‘serious’
  - hospitalised or hospitalisation period extended
  - attended emergency department or specialist
  - life threatening
  - death
  - recovery with sequelae - incapacity/disability
  - congenital anomaly.
- 3255 reports (20%) were for adverse events following immunisation (AEFI)
  - about 7% of the AEFI reports were ‘serious’.

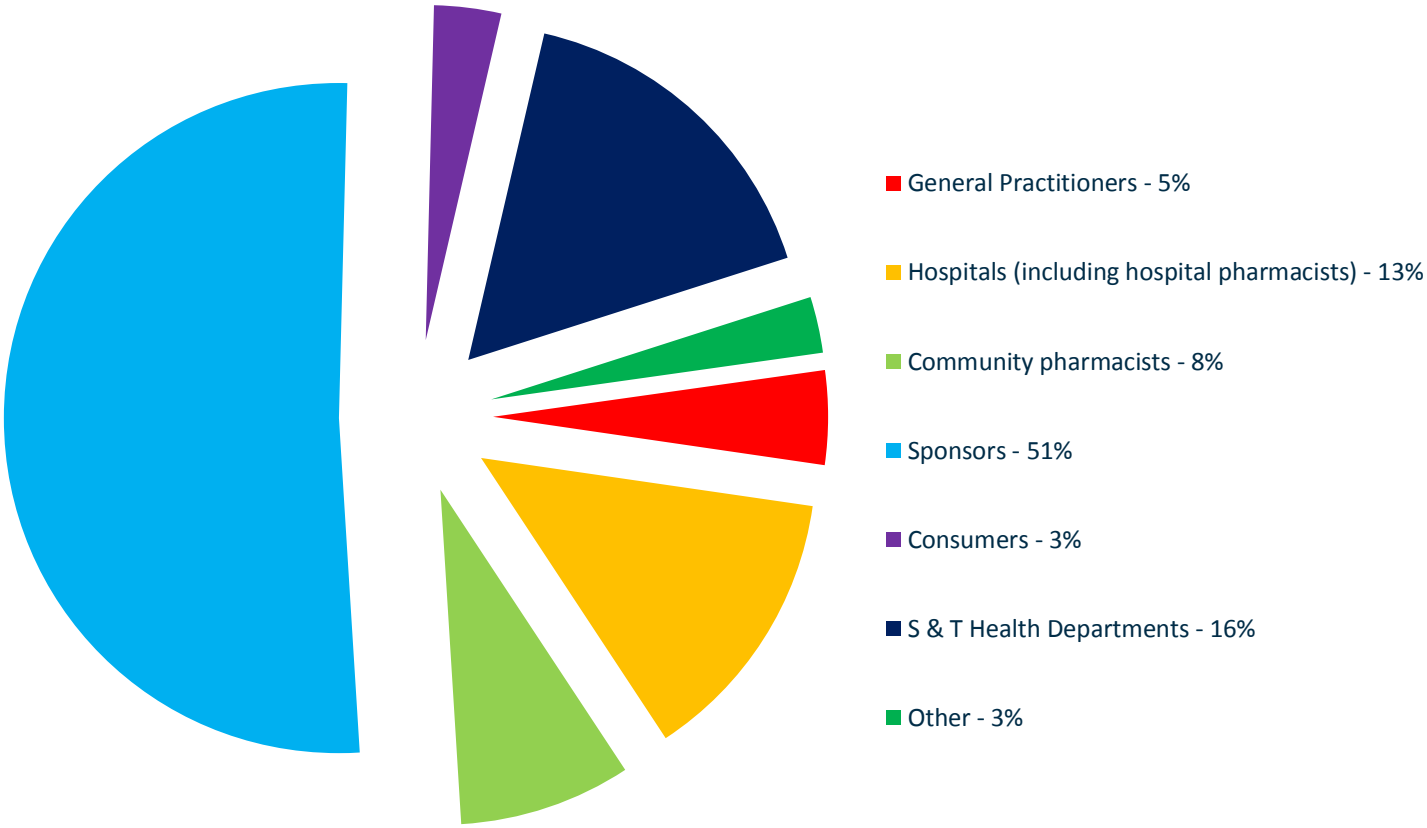
Who reports adverse events?

- 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 (2010-2014)



Sources of adverse event reports received by the TGA in 2014



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
  - GuildLink interface.
- Telephone via NPS MedicineWise Adverse Medicine Event Line – consumers.
- Vaccines – State/Territory Health Departments or agencies (e.g. SAEFVic)
  - various formats.

Entry into database

- Data are entered by staff in the data entry team who:
  - lodge the reports
  - triage them for assessment and coding by:
    - database staff – non-serious 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.

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’ → 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.

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.

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 committees on the safety of medicines (ASCOM) and vaccines (ACSOV)
    - convene Expert Panels for some issues
  - use international data and liaise with other regulators.

Investigation/assessment (continued)

- Initial stage is a safety filter.
  - generally short (3 page) evaluation of the issue
  - standard template
  - 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 – actions taken to mitigate the risks:
  - Alteration of product labelling
    - Product information (PI) and Consumer Medicine Information (CMI)
      - indications, contraindications, warnings, dosage and administration, boxed warnings
    - packaging
  - other changes to conditions of registration
    - role of the RMP
  - product removal, i.e. suspension, cancellation, recall
  - 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.

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

- *Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines* includes mandatory adverse event reporting for sponsors and guidance on pharmacovigilance systems.
  - https://www.tga.gov.au/australian-requirements-and-recommendations-pharmacovigilance-responsibilities-sponsors-medicines
  - https://www.tga.gov.au/pharmacovigilance-guidelines (for other resources).
- Reporting obligations:
  - any significant safety issue, i.e. one that impacts product safety or its benefit-risk profile, must be reported to the TGA within 72 hours
  - serious adverse events must be reported to the TGA within 15 days
  - non-serious adverse events must be recorded in the sponsor's database and included in the PSUR (if required) and provided to the TGA upon 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
  - *Reporting adverse events to medicines and vaccines* brochure (https://www.tga.gov.au/publication/reporting-adverse-drug-reactions)

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