



Australian Government

Department of Health

Therapeutic Goods Administration

TGA pharmacovigilance for biosimilar medicines

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Presentation overview

- Definitions
- Overview of pharmacovigilance at the TGA
- Risk management plans
- Spontaneous adverse event reporting - TGA Adverse Drug Reaction System (ADRS)
- Drugs of Special Interest (DOSI)
- Environmental scanning and international collaboration
- Signal detection, investigation and response

Definitions

- Pharmacovigilance
 - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any drug-related problem (WHO 2002)
- 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
- 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

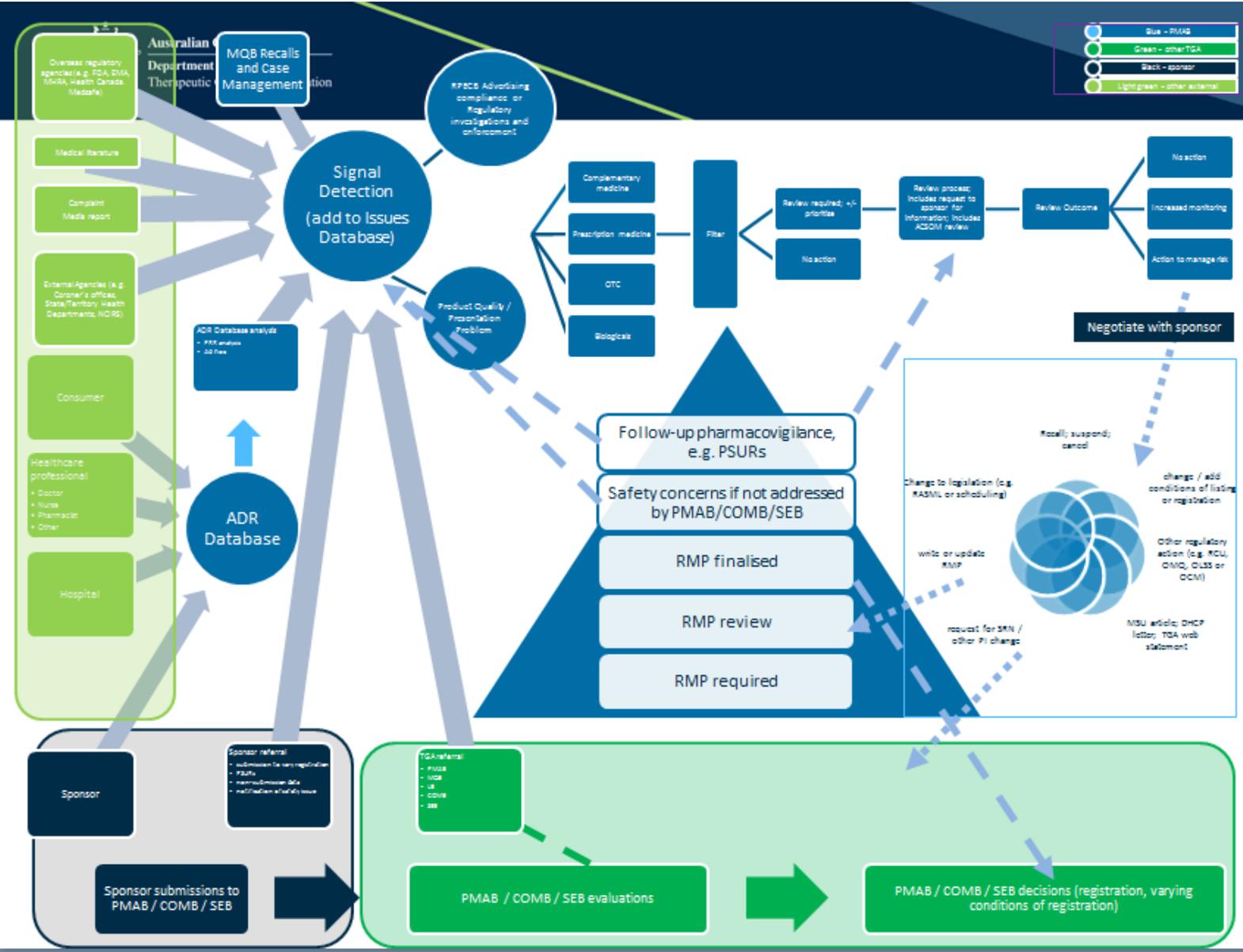
Why pharmacovigilance?

- Identify new (unknown) or change in rates of known adverse events (AEs)
 - Not all AEs are identified in pre-market clinical trials
 - Small numbers so can't detect rare AEs
 - “rule of 3” – need 3N patients to detect an AE with a frequency of 1/N
 - Exclusion criteria → study population differs from population using drug after registration
 - age, sex, pregnancy, comorbidities, concomitant medications
 - Statistical aspects focus on efficacy endpoints not safety
 - Experimental environment – tightly controlled v ‘real world’
 - Relatively short duration of trials – late AEs not identified
- Identify production and other quality issues

Key pharmacovigilance activities at the TGA

1. Risk Management Plan evaluation
2. Monitoring and maintaining the Adverse Drug Reaction System (ADRS) database
3. Drugs of special interest (DOSI) list
4. Environmental scanning of the literature, other regulators and the World Health Organization (WHO)
5. Collaboration with international regulators
6. Evaluating post-market safety information provided by sponsors (e.g. periodic safety update reports, sponsor analysis of signals)

Pharmacovigilance Process



Risk Management Plans (1)

- Sponsors are required to submit a Risk Management Plan (RMP) to the TGA to support any application to register a new biosimilar medicine, or make a major variation of a registered biosimilar (e.g. extension of indication).
- The RMP outlines the risk management system for a medicine once it is available for use in Australia.
- Comprises:
 - Known safety profile from preclinical and clinical studies and post-market activities (if applicable)
 - A summary of safety concerns categorised as ‘Identified’ and ‘Potential’ risks and ‘Missing Information’
 - Information on how these safety concerns will be monitored and mitigated in the Australian context
- Focuses on:
 - Monitoring – Pharmacovigilance Plan
 - Minimising risks associated with the use of the product – Risk Minimisation Plan

Risk Management Plans (2)

- Provides:
 - Coverage of the life cycle of the product
 - Assurance that the known risks related to the use of a medicine have been considered and acted upon
 - Australian context for pharmacovigilance/risk minimisation activities where they differ from overseas RMP activities (Australian Specific Annex)
- Routine risk minimisation activities include:
 - Product Information
 - Consumer Medicines Information
 - Directions for use document
 - The labelling
 - The pack size and design
 - The legal (prescription) status of the product

- Additional risk minimisation activities can include:
 - Education programs for patients
 - Health care professional education programs
 - Dear Health Care Professional letters
 - Controlled access programme

TGA Adverse Drug Reaction System

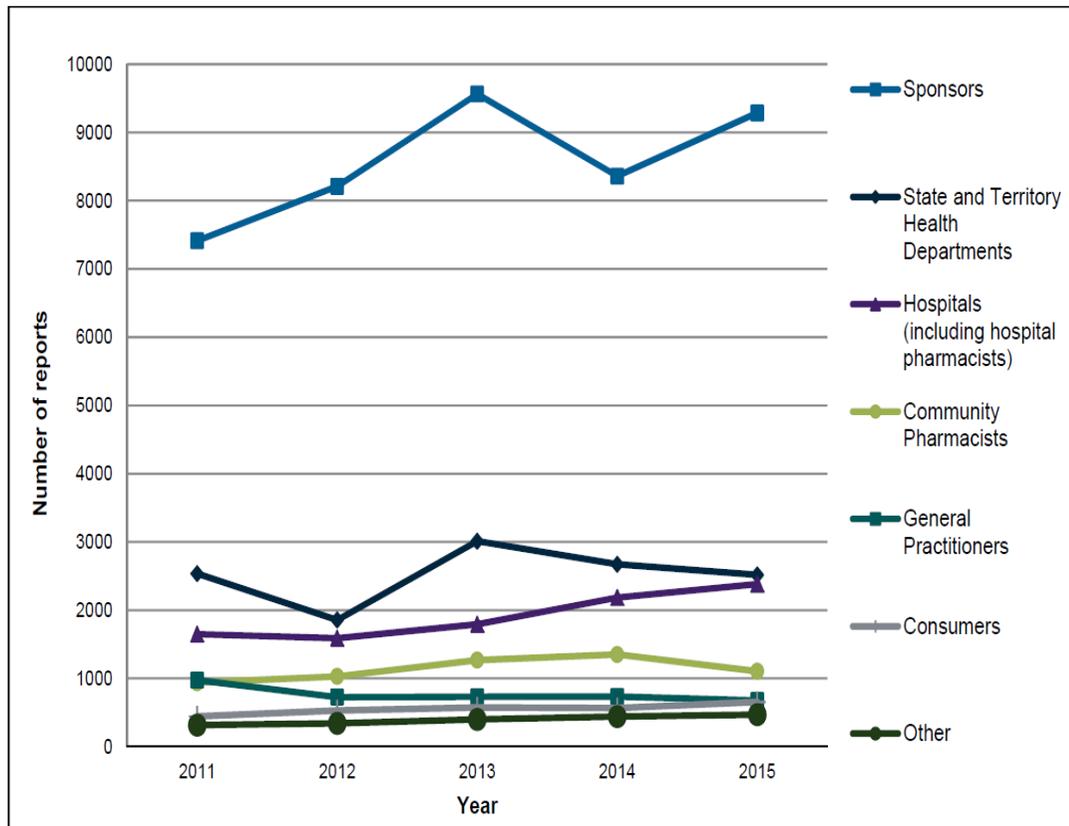
- ADR data collection began August 1964 (post thalidomide)
 - data collection and storage initially paper based; electronic since 1971
- Spontaneous reporting system
 - mandatory for sponsors (within 15 days for serious reactions)
 - voluntary for health professionals, consumers
 - benefits = all drugs, all patients, fast, relatively cheap
 - drawbacks = under-reporting, lack of key information, no denominator
- 18 000 reports received each year
- At 25 November 2016, there were
 - 351,190 individual case safety reports (ICSRs) in the database
 - of which over 326,687 used for routine analysis
- De-identified data publicly available and searchable online via the link to the website - [Database of Adverse Event Notifications \(DAEN\)](#)
- Data provided to WHO global database (Vigibase), which currently holds over 13.7 million ICSRs

How reports are received

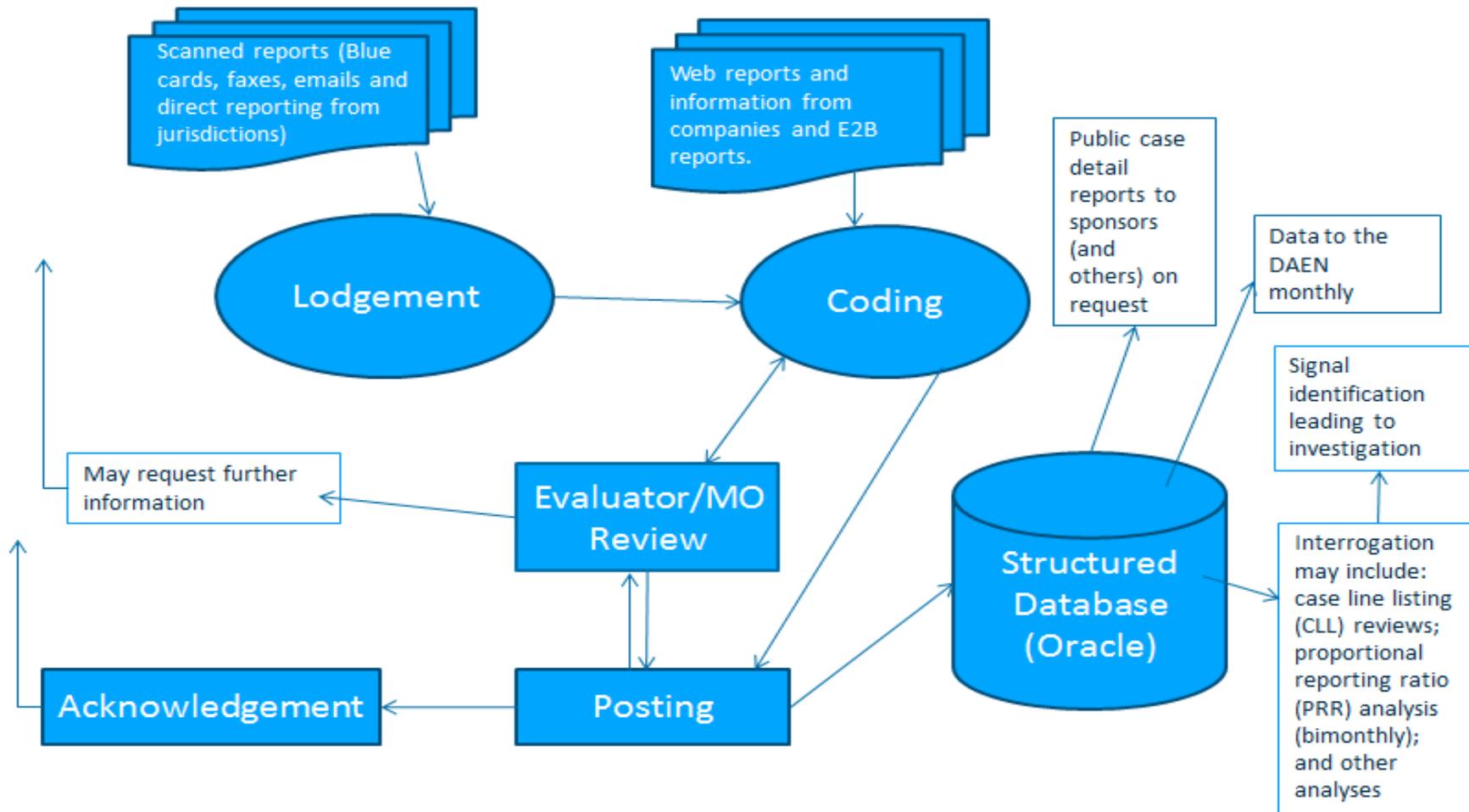
- Blue card - health professionals and consumers

- CIOMS form (international format) - sponsors
- Letters/emails/telephone - health professionals and consumers
- Web reporting via TGA website – sponsors, consumers & health professionals
- Telephone via Adverse Medicine Event Line (NPS) – consumers
- Vaccines – state/territory health departments or agencies (e.g. SAEFVic)
 - various formats

Source of medicine and vaccine adverse events reports



TGA ADRS Database



Disproportionality analysis

- The basis of data-mining in spontaneous adverse event report databases
- Is the reporting rate for a specific reaction for a specific drug different from the specific reaction for other drugs?
- A range of measures of disproportionality (frequentist and Bayesian)
 - Proportional reporting ratio – PRR – Australia and others
 - Reporting odds ratio - ROR - Netherlands
 - Empirical Bayes Geometric Mean - EBGM - US FDA
 - Information Component – IC (Bayesian Confidence Propagation Neural Network (BCPNN) – WHO
- A range of comparators
 - drug versus rest of database
 - drug versus rest of class
 - drug versus drug

PRR calculation (2x2 table)

	reaction of interest	all other reactions	total reports
drug of interest	a	b	a+b
rest of database	c	d	c+d

- PRR= risk in drug of interest compared to risk in rest of database
= $a/(a+b) \div c/(c+d)$
- PRR analysis at the TGA is conducted bimonthly

Drugs of Special Interest (DOSI)

- TGA list of medicines that are under more intensive post-market surveillance
- Newly registered biosimilar medicines are included on the DOSI list
- DOSIs have a lower threshold for signal detection via disproportionality analysis of ADRS data.
- PSURs more frequently reviewed for medicines on the DOSI list
- Review process for removing medicines from the DOSI list

Environmental scanning and international collaboration

- Regularly scan the FDA, EMA, Health Canada and MHRA for new signals
- Also scan the medical literature
- Regular teleconferences with the FDA, Health Canada, HSA Singapore and Medsafe NZ
- Ad-hoc teleconferences and meetings with other international regulators
- No significant safety issues for biosimilar medicines detected or investigated through these activities to date

Post-market data provided by sponsors

- Submission of Periodic Safety Update Reports (PSURs) for specific time period required as condition of registration:
 - Usually submitted on a 6 or 12-monthly basis
 - Contain analysis of reports from clinical trials and spontaneous reporting held in sponsor's global pharmacovigilance database, including analysis of signals detected by sponsor during the reporting period
 - Contains information on international regulatory activities and requests
 - Contains data on international exposure (denominator data)
- Sponsors are also required to notify the TGA of any significant new safety issues that arise, in line with the *Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines*
- The TGA also requests other information from sponsors, including signal analyses, as required

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 Periodic Safety Update Reports (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
 - TGA Advisory committees
 - Convene Expert Panels for some issues
 - Use international data and liaise with other regulators
 - 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
 - Informs the regulatory response

Signal response

- 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 risk management plan (RMP)
 - Product removal – suspension, cancellation, recall
 - Changes to legislation, guidelines etc.
- Signal response - actions taken to mitigate the risks (continued)
 - Communication of important safety and benefit-risk information
 - Sponsor - Dear Healthcare Professional Letters (DHCPLs)
 - TGA - Web statements, Medicine Safety Update (MSU) articles
 - TGA liaison with National Prescribing Service (NPS), professional colleges and other groups

Questions



Useful information

- Useful information can be found via the following websites:
 - [TGA Website](#)
 - [DAEN](#)
 - [Regulation of biosimilar medicines](#)
 - [Therapeutic product vigilance at the TGA](#)
 - [TGA pharmacovigilance guidelines for sponsors](#)
 - [EMA biosimilar guidelines](#)