



Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance: The Australian landscape

TGA perspective

Dr Claire Behm
Director, Signal Investigation Unit,
Pharmacovigilance and Special Access Branch
Medicines Regulation Division, TGA
2017 ARCS Annual Conference

TGA Health Safety
Regulation

Overview

- A reminder of why is pharmacovigilance important
- MMDR review
- Recent legislative changes
- Revised pharmacovigilance guidelines
- Black triangle scheme
- PI reformat
- Adverse event management system
- Use of linked data sets to support pharmacovigilance
- Active surveillance of AEFIs

Why is pharmacovigilance important?

- 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



MMDR review

- **Medicines and Medical Devices Regulation (MMDR) Review**
 - Conducted by an expert panel and made 58 recommendations relating to the regulation of medicines, medical devices, post-market monitoring, complementary medicines and advertising of therapeutic goods.
 - On 15 September 2016, the Australian Government released its response to the MMDR review.
 - The Government accepted the majority of the review's recommendations in full or in-principle and announced a program of reform to facilitate their implementation.
 - Series of recommendations for prescription medicines aimed at facilitating more rapid consumer access to breakthrough medicines via expedited registration pathways (provisional and priority approval), and enhanced post-market monitoring to help ensure patient safety is not compromised.

Recent changes to the Australian pharmacovigilance landscape

- Implementation of a pharmacovigilance inspection program (PVIP), facilitated by:
 1. Amendments to therapeutic goods legislation
 2. Revision of PV guidelines
 3. New PVIP guidelines
- Black triangle scheme
- PI reformat
- Adverse events management system
- Exploration of use of linked data sets to support signal investigation
- Active surveillance of adverse events following immunisation



Overview of recent legislative changes

- Therapeutic Goods Act and regulations now have amended powers to support pharmacovigilance inspections and record keeping requirements.
- **Therapeutic Goods Act 1989, 28(5)(a)** allow an authorised person:
 - (i) *to enter, at any reasonable time, premises at which the person deals with the subject goods, **complies with record-keeping requirements covered by [paragraph \(c\)](#) or (ca)**, or keeps documents that relate to the subject goods; and*
 - (ii) *while on those premises, to inspect those premises and any therapeutic goods on those premises and to examine, take measurements of, conduct tests on or take samples of any therapeutic goods on those premises or any thing on those premises that relates to any therapeutic goods; and*
 - (iii) *while on those premises, to make any still or moving image or any recording of those premises or any thing on those premises; and*
 - (iv) **while on those premises, to inspect, and make copies of, any records kept in compliance with [paragraph \(c\)](#) or (ca); and**
 - (v) **while on those premises, to inspect, and make copies of, any documents that relate to the subject goods; and**
 - (b) *if requested to do so by an authorised person, produce to the person such documents relating to the subject goods as the person requires and allow the person to copy the documents; and*
 - (c) *in relation to each batch of the subject goods--keep a record, at least until the end of the period of 12 months after the expiry date for the goods, of all of the manufacturers involved in the manufacture of that batch; and*
 - (ca) comply, in relation to the subject goods, with any record-keeping requirements that are prescribed; and**
 - (d) *if requested to do so by an authorised person, make any record **kept in compliance with [paragraph \(c\)](#) or (ca)** available to the authorised person for inspection:*
 - (i) *at or before the time the authorised person requests, or (if the authorised person requests) immediately; and*
 - (ii) *either in electronic form or in paper form, as the authorised person requests; and*
 - (e) *comply, in relation to the subject goods, with any reporting requirements that are prescribed;*

Overview of recent legislative changes

- **Therapeutic Goods Act 1989 Section 46A: Searches of certain premises to monitor compliance with Act**

(4) This section applies to:

(a) being premises connected with:

.....

(iv) the importation, export, manufacture or supply of therapeutic goods; or

(v) the keeping of documents relating to the importation, export, manufacture or supply of therapeutic goods; or

(vi) the keeping of records in compliance with paragraph 28(5)(c) or (ca); and

Overview of recent legislative changes

- Therapeutic Goods Regulations 1990 15(A) Conditions of registration and listing of medicines:

*For the purposes of paragraphs 28(5)(**ca**) and (e) of the Act, a person in relation to whom a medicine is registered or listed must comply with the **record-keeping requirements (if any) and the reporting requirements (if any)** set out in the document published by the Therapeutic Goods Administration titled **Pharmacovigilance Responsibilities of Medicine Sponsors**, as in force from time to time.*

Overview of revised pharmacovigilance guidelines

- Main purposes for revision:
 - Transition to a web-based guidance format
 - Improve clarity in the guidelines based on enquiries and feedback from sponsors
 - Strengthen record keeping requirements
- New title: ***Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements***

Consultation on revised pharmacovigilance guidelines

- Targeted consultation closed **17 July 2017**
- Currently in the process of reviewing submissions
- Once the revised pharmacovigilance guideline is finalised, it will be published on the TGA website
- Pharmacovigilance inspections will use these guidelines (and other relevant legislation) to assess compliance of sponsors on pharmacovigilance 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

New information

- Tabulated summary of regulatory reporting requirements
- Aboriginal and/or Torres Strait Islander origin as a new key data element (where possible)
- Additional reporting information related to transmission of infectious agents, orphan drugs and suspended or discontinued products
- Additional guidance about safety contracts and agreements for third-party/external parties
- New record-keeping requirements (in line with EMA requirements):
 - *All safety-related information, including adverse event reports, must be retained indefinitely for the life of the product and for 10 years after its removal from the ARTG to meet the TGA pharmacovigilance requirements.*

Clarification of information

- What, when, how and where to report
- Significant safety issues
- Differences between *Australian Pharmacovigilance Contact person* and *Qualified person responsible for Pharmacovigilance*

Updated information

- Process for notifying/updating details of the *Australian pharmacovigilance contact person* through TGA Business Services (TBS) system (previously via Client details form)
- TGA contact details for reporting
- Layout format
 - First part: Reporting requirements
 - Second part: Guidance on Pharmacovigilance system and best practice



▼ Black triangle scheme

- Provides means to identify new medicines
- Encourages the reporting of adverse events associated with their use
- The symbol and text will appear on the PI and CMI, and TGA-related materials

PI:

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events.

CMI:

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

▼ Black triangle scheme

Inclusion criteria

- All new medicines, except:
 - Biosimilars
 - Seasonal influenza vaccines
- Medicines with a provisional extension of indications
- Extensions of indication into significantly different conditions or patient groups may be included
 - E.g. for an oncology to rheumatology indication

Implementation

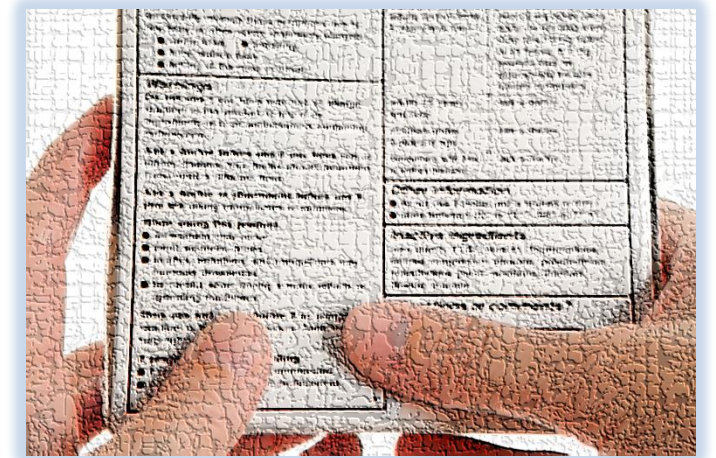
- Scheme starts in **January 2018**
- 5 year duration for standard registration
- 5+ years for provisional registration
 - Provisional registration period ± additional period
- Inclusion automatically lapses at the end of the agreed period
- Intensive communication planned for health professionals and consumers from late 2017 – 2019

▼ Comparison to EU black triangle scheme

- Australian Black Triangle Scheme similar to EU:
 - Wording that accompanies the symbol:
 - the same (excluding reference to information about reporting adverse events in SmPC)
 - Inclusion of symbol on medicine information is similar to EU:
 - Will appear on Australian PI and CMI
 - Inclusion criteria:
 - Biosimilar medicines excluded in Australia, but not in EU
 - In EU, medicines can be included based on PRAC advice
 - Duration of inclusion is the same in EU
 - 5 years in EU for new medicines
 - Duration for ‘conditional approval’ linked to post-market commitments

Product Information reformat

- The Product Information (PI) is being reformatted to:
 - Improve its usability for health professionals, by bringing critical clinical information to the front of the PI
 - indications, dosage and administration, contraindications, precautions, adverse events
 - Align format with European Summary of Product Characteristics (SmPC), and NZ Data Sheet
- Transition to the new format will be over 3 years
 - New medicines and any medicines with new PI information will be in the new format
 - E.g. extended indications, safety updates
- All PIs in the market will be in the new format by the end of 2020



PI reformat – high level changes

Current format

- Name of the medicine
- Description
- Pharmacology
- Clinical trials
- Indications
- Contraindications
- Precautions
- Adverse effects
- Dosage and administration
- Overdosage
- Presentation and storage conditions
- Name and address of the sponsor
- Poison schedule of the medicine
- Date of approval

Proposed format

1. Product Name
2. Qualitative and Quantitative Composition
3. Pharmaceutical Form
4. Clinical Particulars
5. Pharmacology
6. Pharmaceutical particulars
7. Medicine Schedule (Poisons standard)
8. Name and address of the Sponsor
9. Date of first approval (ARTG entry)
10. Date of most recent amendment

PI reformat – detailed changes of interest

Current format

- Name of the medicine
- Description
- Pharmacology
- Clinical trials
- Indications
- Contraindications
- Precautions
- Adverse effects
- Dosage and administration
- Overdosage
- Presentation and storage conditions
- Name and address of the sponsor
- Poison schedule of the medicine
- Date of approval

Proposed format

4. Clinical Particulars

- 4.1. Indications
- 4.2. Dosage and administration
- 4.3. Contraindications
- 4.4. Precautions
 - Use in hepatic impairment, Use in renal impairment, Use in the elderly, Paediatric use, Effects on laboratory tests*
- 4.5. Interactions with other medicines and other forms of interactions
- 4.6. Fertility, pregnancy and lactation
 - Effects on fertility, Use in pregnancy, Use in lactation*
- 4.7. Effects on ability to drive and use machines
- 4.8. Adverse effects
- 4.9. Overdose

PI reformat – detailed changes of interest

Current format

- Name of the medicine
- Description
- Pharmacology
- Clinical trials
- Indications
- Contraindications
- Precautions
- Adverse effects
- Dosage and administration
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- Name and address of the sponsor
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- Date of approval

Proposed format

5. Pharmacology

5.1 Pharmacodynamic properties

Mechanism of Action, Clinical Trials

5.2. Pharmacokinetic properties

Absorption, Distribution, Metabolism, Excretion

5.3. Preclinical safety data

Genotoxicity, Carcinogenicity

Adverse event management system

New and improved Adverse Events Management System (AEMS)

- AEMS will support system to system exchange of adverse event reports using standardised international message formats. This will make it easier for sponsors to send adverse event information to the TGA.
- The new system will also assist the TGA in enhancing its signal management capabilities through more advanced signal detection and data analysis processes.
- Currently the TGA is:
 - evaluating feedback from Sponsors as part of Beta testing of the EDI which is due to conclude at the end of August; and
 - developing an enhanced online AE reporting capability.

Analysis of de-identified health data sets to support pharmacovigilance

- Two feasibility projects in progress:
 1. Prescription sequence symmetry analysis of PBS data to enhance signal detection
 2. Analysis of data from the SAX institute 45-and-up study and linked services datasets to enhance signal verification



The results of these projects will inform future initiatives to use linked datasets to enhance post-market monitoring in Australia

Active surveillance of AEFIs

- AusVaxSafety – A national collaborative active vaccine safety surveillance initiative lead by the National Centre for Immunisation Research & Surveillance (NCIRS) and funded by the Australian Government Department of Health
- Sentinel active participant-based surveillance across more than 156 sites:
 - SmartVax and Vaxtracker - Software programs run by general practitioners and immunisation clinics that send an SMS or email to patients or carers following vaccination
 - STARSS – NHMRC funded study evaluating the use of SMS and telephone follow-up after vaccination
- De-identified information from SmartVax, Vaxtracker and STARSS are combined and monitored by AusVaxSafety to detect safety signals.

AusVaxSafety

- In 2017, AusVaxSafety surveillance is being conducted for the following vaccines and age groups:
 - Influenza vaccine in all ages during influenza season (April–October)
 - Pertussis (whooping cough)-containing booster vaccines in children aged 12 months to <7 years
 - Zoster (shingles) vaccine in adults aged 70–79 years





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