The TGA Pharmacovigilance Inspection Pilot Program
2015-2016

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Overview

• Background to the pilot
• The sponsors involved
• The inspection process
• What was Inspected
• The Findings
• Common Deficiencies
• Feedback
• Next steps
Background to the pilot

- March 2015: TGA pilot program announcement, undertaking voluntary pharmacovigilance inspections in Australia.
- May 2015: TGA dissemination of pilot information to industry for expressions of interest.
- October 2015 - May 2016: 10 volunteer companies took part in the pilot inspection program
The sponsors involved

- **Aim:** To inspect a variety of sponsors in order to understand the broad variations in pharmacovigilance systems currently in place in Australia.

- Volunteers included:
  - Large multinational companies
  - Australian owned and based companies
  - Smaller biotechnology companies
  - Generic companies
  - Complementary /herbal medicine companies
The Products Involved

- Registered Medicines
- Listed Medicines
- OTC
- Complementary
- Vaccines
- Innovative medicines
- Generic medicines

- Topical products
- Oral products
- Nasal delivery products
- IV products
- Medicines with RMPs/PSURS
- Medicines without RMPs/PSURS
The Inspection Process

Pre-Inspection

Approximately **one month prior** to inspection a **draft agenda** and **initial document requests** for the inspection were sent to company.

Several documents were requested to be provided prior to inspection to allow for **inspector preparation**.
The Inspection Process

Inspection

- **First day of the inspection**: Opening meeting conducted to discuss the inspection process and the background to the inspections and to allow for a company overview of the systems in place.
- **Throughout the inspection**:
  - Interview sessions were conducted to gain an understanding of the pharmacovigilance processes undertaken by the company.
  - Followed by document requests to verify/provide evidence of these company processes.
  - In between interview sessions inspectors would review documents.
- **Final day of the inspection**: a verbal overview of any deficiencies identified during the inspection was given to the company in the form of a closing meeting.
The Inspection Process

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The Inspection Process

Post-Inspection

- **Four weeks after** last document was received by the inspector, a **formal inspection report** was provided to the company.

- The company then had four weeks to respond to the findings
  - formal **Corrective and Preventative Action (CAPA) plan** (template provided)
  - carry out any actions required

- The proposed CAPAs were assessed by the inspectors.

- Any changes or additions deemed necessary were negotiated.

- Once agreed by both parties, the inspection was closed out.
What was inspected?

1. ADR collection and processing
2. Processes for ongoing monitoring of safety
3. PSUR production and coordination
4. Maintenance of Reference Safety Information
5. The Australian person responsible for pharmacovigilance
Relevant Legislation

During the inspection compliance with currently applicable Australian pharmacovigilance regulations and guidelines was assessed:

- **Therapeutic Goods Regulations 1990 (Regulation 15A)**
- **Therapeutic Goods Act 1989 (Section 28 (5e), 29A and 29AA)**
- **Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines (Version 1.3, June 2014)**
- **The Conditions- standard and specific applying to registered or listed therapeutic goods**
Grading of deficiencies

Critical Deficiency
- A deficiency in pharmacovigilance practice or process that has, or may significantly adversely affect the safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.
- Also occurs when it is observed that the sponsor has engaged in fraud, misrepresentation or falsification of data.

Major Deficiency
- A deficiency in pharmacovigilance practice or process that could potentially adversely affect the safety or well-being of patients or that could pose a potential risk to public health or that represents a significant violation of applicable legislation and guidelines.
Grading of deficiencies

Other Deficiency

- A deficiency in pharmacovigilance practices or processes that cannot be classified as either critical or major, but indicates a departure from good pharmacovigilance practice. Includes deficiencies that would not be expected to adversely affect the safety or well-being of patients.
- A deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical.
The Findings

Number of findings:
• Critical findings - 0
• Major findings - 25
• Other findings - 18
The Findings

- Australian PV person roles and responsibilities
- Deficiencies in procedural documentation
- Ongoing monitoring processes
- Submission of PSURs
- Significant safety issues communication
- Maintenance of RSI
- AE case collection and processing

Bar chart showing the findings with categories and corresponding bars for critical, major, and other issues.
Some common deficiencies identified

AE case collection and processing

• Late submission and non-submission of serious Australian cases to the TGA
  – All serious adverse reactions occurring in Australia must be reported to the TGA within 15 days of receipt by the sponsor (Pharmacovigilance Guidelines).

• Non-conservative seriousness assessments
  – Seriousness assessments should be an independent process to medical evaluation, causality and validity of the case i.e. based on the adverse event alone
  – Where outcomes or treatment information is not available, a conservative approach should always be taken
Some common deficiencies identified

AE case collection and processing

- **Lack of due diligence in identification of AEs and special situation reports**
  - Care should always be taken to determine if an enquiry involves an adverse event for collection and reporting purposes.
  - Often relating to MI enquiry cases

- **Deficiencies in the pharmacovigilance contracts and training of vendors**
  - Omissions, errors and discrepancies in contracts for post-marketing initiatives (e.g. patient support programs and market research), sales, promotion and distribution partners.
  - Contracts must ensure all safety information is collected and communicated to the sponsor effectively; include provisions for reconciliation, training.
Some common deficiencies identified

Maintenance of Reference Safety Information

- Delays in updating Australian Product Information documents
  - From when the sponsor became aware of the need to initiate a reference safety change
  - TGA expectation is a variation will be submitted within 6 months from identification of any safety related issue
- Delays in updating product CMI documents
  - CMI document needs to be changed within two weeks of the date of the changed PI (Conditions of Registration)
Some common deficiencies identified

Communication of significant safety issues

• Deficiencies in communicating significant safety issues
  – Sponsors must report all significant safety issues to the TGA within 72 hours (Pharmacovigilance Guidelines)
  – Significant safety issues may include:
    ▪ issues from review and analysis of AR reports occurring outside Australia
    ▪ action taken by a foreign regulatory agency
    ▪ identification of new risk factors that may impact on the safety or benefit-risk assessment of the product
Some common deficiencies identified

Submission of PSURs

• Schedule of PSUR submissions
  – The intent of the *Conditions of Registration* is that PSURs cover periods aligning with the Australian approval date i.e. first PSUR should cover a 6 or 12 month period from the date of approval
  – It is a requirement that sponsors request the condition to be varied if they are going to deviate from this
  – In several instances, PSURs submission timelines had been adjusted to align with international birth dates without any formal approval to vary the conditions of registration
  – The TGA is currently reviewing this requirement
TGA Feedback

• Pilot was an exercise to offer education and guidance to sponsors
  – Foundation of TGA’s Regulatory Compliance Framework
• Examples of excellent pharmacovigilance processes in place
  – Organised AR case collection and processing procedures
  – Comprehensive ongoing monitoring processes
  – Sufficient training of staff
• Commitment by companies to improve pharmacovigilance systems
Sponsor Feedback

• Participating companies were asked to fill out a questionnaire
  – Regarding their experience of the inspection
  – Will help shape any future program in Australia
• Responses on a whole have been positive:
  – helpful in identification of areas in pharmacovigilance system where improvement was needed
• time-consuming and challenges with time-zone differences.
Next Steps

To be determined…

• Feasibility of a national pharmacovigilance inspection program
• Any decisions and the implementation of an Australian program will involve an industry consultative process.
• PV inspections will continue to use a risk-based approach that might include both random and targeted inspections
• High level of sponsor compliance to good pharmacovigilance systems required due to increased importance of post-market monitoring
Summary

• Background to the pilot
• Characteristics of sponsors who participated
• The Inspection Process
• What was inspected
• The findings
• Common deficiencies
• Feedback
• Next steps