Pharmacovigilance Inspections
Pharmacovigilance requirements inspected and example findings

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Part 2: What we inspect
Overview

• Pharmacovigilance system expectations
• What we inspect
  – Management of adverse reaction reports
  – Ongoing monitoring of your medicines
  – Significant safety issues
  – Maintenance of Reference Safety Information
  – Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs)
  – Quality Management Systems
  – Contracts and agreements
• How to prepare for an inspection
Pharmacovigilance system expectations

• You should have a robust and effective pharmacovigilance system in place that allows you to:
  – meet all pharmacovigilance recommendations and requirements described in the *Pharmacovigilance responsibilities of medicine sponsors - Australian recommendations and requirements* (Pharmacovigilance Guidelines) and applicable legislation.

• The TGA expects differing levels of complexity of pharmacovigilance systems proportionate to a company’s product portfolio (i.e. prescription/OTC/comp med), sales volume and volume of reports received.
What we inspect

• Inspections assess the **appropriateness** and **compliance** of your pharmacovigilance system to the Australian guidelines and requirements.
• Aspects of the system analysed will vary depending on
  – the system in question
  – the products available on the ARTG (listed vs registered)
  – the medicine’s specific safety requirements (i.e. PSURS and RMPs)
  – any specific concerns we might have
What we inspect

• Areas we may inspect include:
  – Management of adverse reaction reports
  – Ongoing monitoring of your medicines
  – Reporting of significant safety issues
  – Maintenance of Reference Safety Information
  – Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs)
  – Quality Management Systems
  – Computer system validation
  – Oversight of the Australian person responsible for PV
  – Contracts and Pharmacovigilance agreements
Management of adverse drug reactions (ADRs)

- We will inspect your overall collection and management of adverse drug reactions.
- This will include:
  - the **collection and collation** of reports from all sources and sites
    *including but not limited to cases reported via medical information enquiries, international literature, social media and the internet, market research programs, patient support programs, voluntary patient registries, post-registration studies and partners*
  - the **assessment** (validation, seriousness, expectedness and causality), **coding and processing** of reports
  - **follow-up** and **outcome recording**
  - **reporting** within the specified timeframes to the TGA, where required
  - **record keeping** and **archiving** of adverse drug reaction reports and data
Example findings - ADR management

1. *Late ADR reporting*

   - Serious adverse reaction cases received from a sales representative were identified that were reported to the TGA 30 days after receipt by the sponsor – this occurred as the ADRs had not been reported by the representative according to current processes.

   - All serious suspected adverse reactions occurring in Australia MUST be reported to the TGA within 15 days of receipt by the sponsor.
Example findings - ADR management

2. Inappropriate seriousness assessment

- Spontaneous cases were identified in an inspection that were assessed as non-serious and therefore not reported to the TGA, due to lack of information being reported. Reaction terms included blindness, anaphylaxis, hepatitis C, renal failure and cancer.

  - Seriousness assessments should be an independent process to medical evaluation. Where outcome or treatment information (e.g. hospitalisation) has not been provided, a conservative approach should be taken and the assessment should be based on the adverse reaction reported alone. Consequently any medically important reaction should be considered serious, where further details are unknown, in accordance with the Australian Pharmacovigilance Guidelines.
Example findings - ADR management

3. **Deficiency in identifying ADRs from complaints and enquiries**
   - ADRs were identified in Product quality complaint cases that had not been collected by the sponsor and thus not included in the safety database. For example “the tablet was harder to swallow than normal and made me go all shaky and vomit”.
   - It was identified in medical information enquiry cases that reasonable steps had not been taken to determine if an AE or a special situation event, including off-label use, had occurred. For example “Can you tell me if low blood pressure is a side effect of medicine X?”, “Is this medicine safe to use in pregnancy?”, “What is the dose recommended for use in a 3 year old?”
   - Care should always be taken to determine if an enquiry involves an adverse event or special situation report for collection and reporting purposes in accordance with best pharmacovigilance practice. This ensures that all potential safety information is being collected, reported and evaluated in ongoing analyses of the benefit-risk balance for a medicine.
Example findings - ADR management

4. Deficiency in monitoring literature reports
   - Several literature reports were identified by the inspector that contained potential ADRs that had not been collected or collated by the sponsor, either for ADR reporting or ongoing monitoring purposes.
   - The result of weekly searches was not documented nor reproducible and staff completing this task had not received appropriate training in literature searching strategies.
   - The search strategy and process used was considered inadequate as it did not contain generic medicine names and did not encompass relevant journals.

   ▪ You should be undertaking regular—no less than weekly—systematic literature review of widely used reference databases (such as Medline, Excerpta Medica or Embase) to identify, report and record adverse reaction reports and significant safety issues. You should use both trade name and generic names of the medicines in your search strategy.
   ▪ Your procedures for monitoring literature should sufficiently capture up-to-date and comprehensive safety information associated with your medicines.
Ongoing monitoring of medicines

- We will assess the ongoing analysis of the risk/benefit profile of your medicine(s) during the post-authorisation period.
- We will include review of your:
  - use of **relevant information sources** for signal detection
  - appropriately applied methodology concerning analysis
  - examination of processes, decision-making, communications and actions relating to signals investigated
  - appropriateness of investigations and follow-up actions such as the implementation of recommendations following data review
  - timely identification and provision of complete and accurate data, in particular in response to specific requests for data from the TGA
Example Findings - Ongoing monitoring

1. **Deficiency in database search strategy**
   - When investigating a signal of “thrombocytopenia” the database search strategy used to identify relevant cases for analysis did not include all relevant MedDRA terms e.g. “decreased platelet count”.
   - In addition non-valid cases (where a drug-event pair was available) and data from legacy safety systems were not included in the ongoing monitoring process.
     - Evaluation of the risks benefits profile of a medicine should be on the basis of full information i.e. all relevant information should be included in analyses. One medical concept may be coded in different ways. When analysing signals, it is important to consider all the MedDRA codes that may relate to the medical concept so that all relevant cases are reviewed. Erroneous conclusions may be drawn on the basis of an incomplete dataset.
Example Findings - Ongoing monitoring

2. **Deficiency in signal detection**
   - *The sponsor had not implemented a formal and routine procedure for signal detection as they considered their product well established with a known safety profile.*
     - Ongoing provision to the TGA of any information relevant to an identified change to the benefits and risks afforded by a medicine is required. Changes in risk-benefit balance may occur at any point in time in a product lifecycle. New products entering the market may impact safety of older products (e.g. interactions).
     - Signal detection should occur on a regular basis for the lifecycle of the medicine in order to detect any signals that may arise.
Example Findings - Ongoing monitoring

3. Deficiency in signal detection analyses
   - A sponsor of medicines with a large market share were undertaking signal detection by manually reviewing cases. Due to the large number of cases being manually reviewed potential signals were being missed.
     - There should be defined criteria and thresholds with which to identify a signal, whether qualitative or quantitative. These methods should also be relevant and suitable for the data set they are aimed at, for example, complex disproportionality analyses should not be applied to limited datasets, and qualitative methods should not be applied to very large datasets.
Significant Safety Issues

• We will assess the identification and reporting of significant safety issues.
• This will include:
  – The examination of processes, decision-making, communications and actions relating to a specific trigger and/or product safety issue
  – The notification to the TGA of significant safety issues that are identified locally and internationally within the specified timeframes
Example Findings - Significant Safety Issues

1. Non-reporting of significant safety issues
   - Two events were identified during the inspection that would be considered significant safety issues by the inspectors but had not been reported as such by the sponsor. The sponsor was in the process of updating Australian Reference Safety Information in relation to these issues but had not yet notified the TGA:
     - The EMA PRAC had recommended the addition of a contraindication and a precaution to a sponsor’s medicine following an increased number of reports of cardiovascular adverse events in Europe.
     - The FDA had published a safety alert for an entire class of medicines, mandating a black box warning to warn of the risk of concomitant use with another commonly used medicine which may increase the risk of a serious adverse event.

Sponsors MUST report all significant safety issues to the TGA within 72 hours of awareness
Reference Safety Information (RSI)

• We will assess a sponsor’s handling and maintenance of reference safety information, including company core safety information, minimum product information, labels, PIs and CMIs.

• We will specifically review:
  – how you maintain any reference safety information to ensure product information is up-to-date and in line with current scientific knowledge
  – that required safety updates are promptly identified:
    – Signal detection and evaluation outputs.
    – Comparison with innovators.
    – Competent Authority requests from the TGA and internationally.
  – the process and timelines for implementation of new/updated reference safety information, including internal distribution and external publication
Example Findings - RSI

1. **Delays in updating RSI**
   - Delays in updating Australian Product Information (PI) documents were identified ranging from 8 months to three years after the sponsor had verified individual safety signals. It was considered that such delays may pose a safety risk to the Australian public.
   - In addition, delays in updating product Consumer Medicine Information (CMI) documents, outside of the required two week timeframe were identified.
     - TGA expects that a variation to amend the PI will be submitted as soon as possible and within 6 months from identification of any safety related issue, in order to ensure that the PI is kept up to date with the current safety information. The 6 month timeline is consistent with EU expectations and good pharmacovigilance practice.
     - The CMI document MUST be amended to reflect an amended PI within two weeks of the date of the changed PI (Conditions of Registration).
Example Findings- RSI

2. Deficiencies in disseminating updated RSI
   
   - *It was identified that after approval of the variation by the TGA, the sponsors had not updated public facing websites with the new PIs, therefore health professionals and consumers would be accessing outdated PIs and CMI*s.*
   
   - *In addition the new PIs and CMI*s had not been internally disseminated and personnel may therefore be using outdated information to educate or respond to product enquires.*

   - Processes and timeframes need to be in place to implement any of new/updated reference safety information, including internal distribution and external publication of these documents and correlating adjustment of minimum product information and medicines information standard response where relevant.
PSURs/PBRERs and RMPs

- We will assess the preparation of Periodic Safety Update Reports/Periodic Benefit-Risk Evaluation Reports (PSURs/PBRERs)
  - **completeness and accuracy** of the data included, appropriateness of decisions concerning data that are not included
  - addressing safety topics, providing relevant analyses and actions
  - **timeliness** of submissions
- We will also analyse the implementation, ongoing review and adherence to risk management plans (RMPs) commitments and other safety commitments (this may include registries, enhanced surveillance or traceability systems), where relevant
Example Findings - PSURs

1. **Review of incomplete case data in PSUR**

   - The sponsor ran a PSUR ADR case report search in their database which captured all ADRs received during the period of the report which were considered related to the product by the reporter. However, it was identified during an inspection that a sponsor had migrated approximately 20,000 case reports from Database X to Database Y. Due to an error, the fields “unlikely” and “not reported” were mapped to the field “No” when the migration occurred and these cases now appear as unrelated in the new database. Therefore, the most recent PSUR did not contain all cumulative cases previously assigned (in database X) a causality of “not reported” or “unlikely”.

   - **PSURs MUST be complete and contain accurate data, in order to meet the conditions of registration**
Example Findings - PSURs

2. **Missing safety information in PSURs**
   - The PSUR reviewed for product Y lacked information on pregnancy and off label use.
   - In addition the information provided on the signals reviewed and subsequently determined not be signals was not sufficient to describe their assessment and there was no discussion of safety findings reported in published literature.
   - The PSUR submitted was therefore not considered a comprehensive review of the products risk safety profile.
     - **PSURs MUST be complete and contain accurate data, in order to meet the conditions of registration.**
Example Findings - RMPs

1. **RMP non-compliance**
   - It was identified during an inspection that the RMP for a sponsor had an additional risk minimization measure - to provide education material to HCPs and to patients to ensure awareness of signs and symptoms suggestive for opportunistic infections. The company was not able to provide evidence that such material was being provided to either HCPs, and there was no documentation surrounding distribution. The sponsor could not prove they had complied with their RMP commitment for this measure.
     - RMP commitments MUST be met as agreed with the TGA on product registration
We will assess the Quality Management System in place to ensure the suitability and consistency of your pharmacovigilance processes.

- We will review:
  - whether **up-to-date and comprehensive policies and procedures** are in place regarding your role and responsibilities in relation to your pharmacovigilance system
  - the **accuracy, completeness and maintenance of records**
  - the **quality and adequacy** of your staff’s **training, qualifications** and **experience**
Quality Management System (QMS)

- We will review (cont’d):
  - the **coverage** of your pharmacovigilance quality system and your **adherence** to it, including quality control and quality assurance processes
  - the fitness for purpose of **computerised systems**
  - the **person responsible for fulfilling your pharmacovigilance obligations in Australia**, their roles and responsibilities (such as access to the quality system, performance metrics and audit and inspection reports) and their ability to take action to improve compliance
  - **Record-keeping** of safety data
Example Findings - QMS

1. **Deficiency in company Standard Operating Procedures (SOPs)**
   - Pharmacovigilance SOPs reviewed did not reflect current PV processes and did not contain timeframes for reporting of ADRs or significant safety issues.
   - In addition the collection of special situation reports including exposure during pregnancy and breastfeeding, lack of efficacy, overdose, abuse, off-label use, misuse, medication error or occupational exposure were not documented in sponsor procedures. Failures to collect such reports were identified during the inspection.
     - SOPs should document PV processes to ensure consistency and compliance with recommendations and requirements.
Example Findings - QMS

2. **Non-compliance in record-keeping requirements**
   - It was identified that safety information, including historic ADRs associated with a medicine acquired recently by the sponsor was not available, having not been transferred to the new sponsor of the medicines appropriately.
     - A sponsor MUST hold all data pertaining to the safety and pharmacovigilance activities of the medicine indefinitely for the life of the medicine and for 10 years (registered) or 5 years (listed) after its removal from the ARTG.
Contracts and Agreements

• We will assess whether contracts and agreements with all relevant third parties (i.e. any external person or organisation who may market, distribute, manufacture, conduct research or carry out any pharmacovigilance activities related to your medicine) reflect pharmacovigilance responsibilities and activities, and are being adhered to.

• Contracts with external parties who may receive safety information for any of a sponsor’s medicines should stipulate the pharmacovigilance roles and responsibilities of all parties to ensure that all safety information is being collected and communicated to the sponsor effectively.

• Training, if relevant, should also be provided to external parties to ensure they are aware of their pharmacovigilance obligations.
Example findings - Contracts and agreements

1. Lack of safety contracts and agreements
   - Examples of external market research providers were identified who were undertaking research for a sponsor, with no contracts in place specifying their pharmacovigilance responsibilities and the requirement to collect of safety information including ADRs.
   - Additionally, no training on PV responsibilities had been given to these providers.
   - The sponsor had no assurance that all safety data was being collected and collated and thus reported in line with regulatory reporting requirements.

   ▪ Sponsors should have detailed pharmacovigilance agreement in place with third party that includes explicit roles and procedures such as what safety information is to be collected and how it is to be exchanged, including timelines, reconciliation and reporting responsibilities.
   ▪ External companies should be appropriately trained and overseen.
Example findings - Contracts and agreements

2. **Deficiency in safety contracts**
   - Several serious adverse events were identified that had not been reported on review of medical information enquiries. On further investigation it was noted that the contract with the external medical information provider was deficient in its detail:
     - There was no timelines for the exchange of data
     - There was no provision for the exchange of safety data in special situations (e.g. pregnancy, misuse, off-label use)
     - Reconciliation activities are not adequately described and were not being conducted
     - No training had been provided to the contracted party to ensure they are aware of their PV obligations

   - contracts and agreements with all relevant third parties should ensure that all safety information is being collected and communicated to the sponsor effectively and reflect their pharmacovigilance responsibilities and activities.
How to prepare for an inspection *(a few pointers)*

- Ensure you have nominated an Australian contact person for pharmacovigilance to the TGA.
- Ensure an appropriate quality management system is in place as a basis for an effective PV system - including up-to-date SOPs, training and auditing programs.
- Ensure all potential sources are being monitored for ADRs - including but not limited to marketing programs, medicines information, product quality complaints, literature, company sponsored internet sites and social media, post market clinical trials etc.
- Ensure you have a robust and secure system to collect, process and analyse medicine safety data.
- Ensure all serious Australian ADRs and significant safety issues are being reported to the TGA within required timeframes.
- Ensure there are procedures in place to receive notification of significant safety issues from global counterparts.
How to prepare for an inspection *(a few pointers)*

- Ensure **ongoing monitoring for safety signals** is occurring on a regular basis
- Ensure you have **safety agreements** in place with required partners and contractors
- Ensure **PSURs** are complete and submitted on time if required
- Ensure any **RMP commitments** are being met
- Ensure the **Australian person responsible for pharmacovigilance** has appropriate oversight of the system
- Ensure **CAPA** from any previous pharmacovigilance inspection has been completed
- Ensure all **safety data** is being **retained** indefinitely for the life of the product and for 10 years (registered) 5 years (listed) after its removal from the ARTG
Questions?

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