Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance inspections

Update on the PVIP, learnings, helpful tips and workshop

Sarah May (Lead), Saqif Shams and Kasia Hoffler
Pharmacovigilance Inspectors
Risk Management Plan Evaluation
Pharmacovigilance and Special Access Branch

TGA ARCS Pharmacovigilance workshop
27 March 2019 Canberra

TGA Health Safety Regulation

Australian Government
Department of Health
Therapeutic Goods Administration

Meet the inspector team

- Sarah May – lead pharmacovigilance inspector
- Saqif Shams – pharmacovigilance inspector
- Kasia Hoffler – pharmacovigilance inspector
- My Di Luu – pharmacovigilance inspector

Outline

- Update on the PVIP
- Practical tips for inspections
- Inspection experiences from an inspectee
- Workshop – developing a CAPA plan

Update on the Pharmacovigilance Inspection Program (PVIP)

The PVIP

- Commenced **1 September 2017**
- First inspection under the program undertaken January 2018
- Conducted **twelve inspections** under the program to date
- Have inspected sponsors of innovators, generics, biosimilars, OTC and complementary medicines

PVIP metrics report

- The first report was published on 20th March 2019 and covers **1 September 2017 to 31 December 2018.**
- Available at https://www.tga.gov.au/pharmacovigilance-inspection-program-metrics-report-sep-2017-dec-2018
- The report contains the following information:
  - Summary of inspections conducted, including type of inspections, types of sponsors and number of findings
  - Description of inspection findings by topic area
  - Details of the common areas of findings
  - Comparisons of inspection findings over time
- Reports will be published **annually** covering a 12 month period hereafter
- All information has been de-identified

PVIP metrics report

Reporting period	1 September 2017 to 31 December 2018
Number of inspections	10
Types of inspections	10 Routine inspections Nil For-cause inspections Nil Re-inspections
Inspection findings	Nil Critical deficiencies 50 Major deficiencies 29 Minor deficiencies

Deficiency definitions

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, 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.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

PVIP metrics report

Areas of findings	Critical (0)	Major (50)	Minor (29)
Management of significant safety issues	-	9	-
Collection and collation of adverse drug reactions	-	12	3
Management of adverse drug reactions	-	9	-
Ongoing safety evaluation	-	5	5
Management of reference safety information	-	10	1
Risk management	-	1	3
Australian pharmacovigilance contact person and the QPPVA		1	
Record-keeping requirement		-	1
Quality management system	-	1	11
Other post-approval commitments	-	2	5

PVIP metrics report

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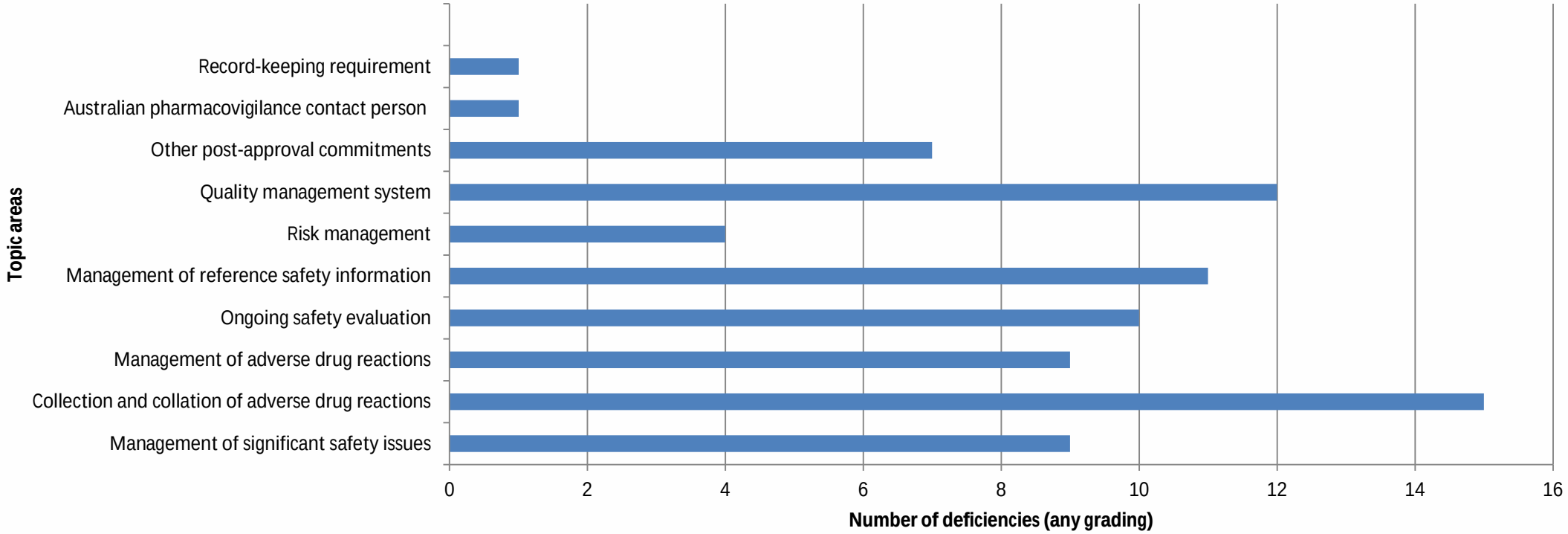
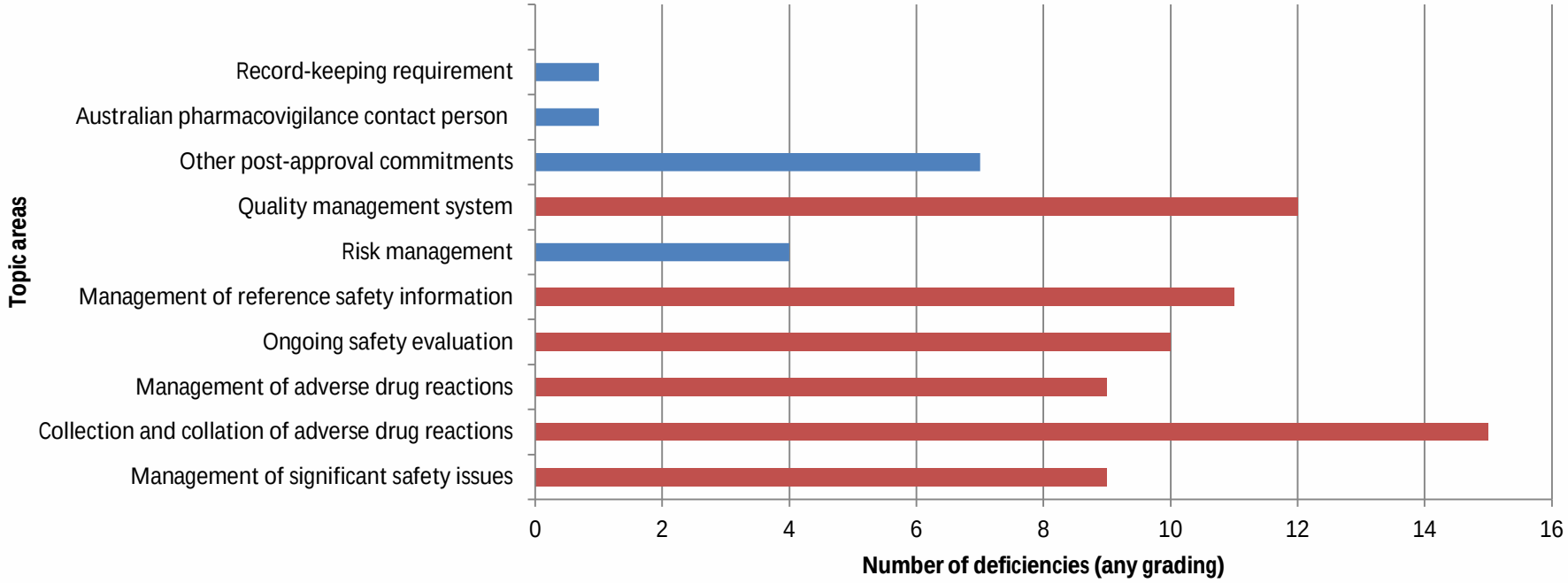
PVIP metrics report



PVIP metrics report



Common areas of findings

1. Management of significant safety issues
2. Collection and collation of adverse drug reactions
3. Management of adverse drug reactions
4. Management of reference safety information
5. Quality management system

Common areas of findings

Management of significant safety issues

- Failure to notify the TGA of significant safety issues
- Late notification of significant safety issues outside the regulatory 72 hours

Common areas of findings

Management of significant safety issues

- A significant safety issue is considered to be any **new important safety issue** or **validated signal** that may **impact on the risk-benefit profile** of a medicine.
- Our definition of a "validated signal" is in line with that stated in the Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1):
  - *"Validated signal: A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal."*
- **Use your clinical and profession judgement**
- Not necessarily a **confirmed signal**
- Depending on the potential seriousness, can include requests for information by comparable international regulator regarding a **potential signal**, or early safety information prior to evaluation completion.
- **Be conservative, contact us for advice**

Common areas of findings

Collection and collation of adverse drug reactions

- Case collection, including monitoring, identification and reconciliation
- Spontaneous sources of safety data e.g. medical information, product quality complaints
- Literature searching
- Solicited sources of safety data, including patient support or market research programs
- Safety data exchange agreements

Common areas of findings

Management of adverse drug reactions

- Case processing, including data entry, coding, causality and seriousness assessment, follow-up and reporting
- Data management, including migration of safety data

Common areas of findings

Management of reference safety information

- Maintenance of reference safety information, including the Company Core Data Sheets, Product Information (PI) and Consumer Medicine Information (CMI), minimum PI and package leaflets
- Maintenance of safety information on sponsor websites and social media
- Dissemination and communication of Australian Reference Safety Information (internally and externally)

Common areas of findings

Quality management system

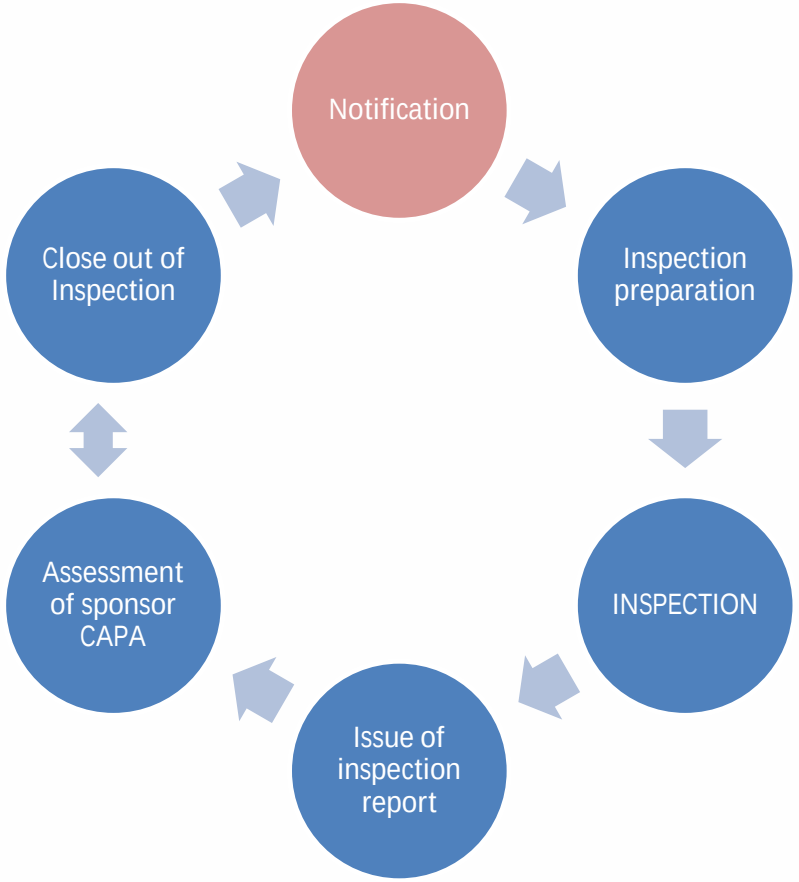
- Procedures, record management, pharmacovigilance training
- Audit and deviation management, including Corrective and Preventive Action management
- Information technology systems and applications

What next?

- Understand your Australian PV requirements and responsibilities
- Review your PV system – start with the common areas of findings discussed
- Continually review and improve your PV system
- Be inspection ready at all times

Practical tips for inspections

Pharmacovigilance Inspection Lifecycle



Practical tips for inspections

Pre-inspection

- ***Following TGA notification of inspection (6-8 weeks):***
  - nominate a main contact person for the inspection
  - confirm the inspection dates with the TGA as soon as possible
  - complete the Australian Pharmacovigilance Systems Summary (APSS) – due 4 weeks from notification
  - decide on the preferred inspection site
    - ensure safety database and QMS are readily accessible so staff are able to run reports and extract data upon request
    - tele/video conferencing, inspection room, printing facilities
  - ensure all staff are aware of and prepared for the inspection

Practical tips for inspections

Pre-inspection

- ***Submission of pre-inspection documents (Sheet A):***
  - single zip file on a USB, courier to TGA office (preferred)
  - e-mail to pharmacovigilance.inspections@health.gov.au
  - Health Data Portal – register using AUSkey (testing phase)

Practical tips for inspections

Pre-inspection

- ***Inspection plan:***
  - Organise which staff will be attending what interview session
  - Inform the TGA of any tele/video conferencing necessary with global staff
  - Book the meeting room

Practical tips for inspections

During Inspection

- ***Interview Sessions***
  - Ensure that staff who are directly performing the role for the process being audited are present in the inspection room (not just business unit managers)
  - Ensure all company staff are aware of the inspection in progress – anyone may be requested to speak to an inspector at any time
  - If staff cannot attend in-person (e.g. global), interview via tele/video conference is acceptable

Practical tips for inspections

During inspection

- ***Document requests***
  - Assign a person to manage all the document requests
  - Ensure your computer system allows data extraction onto a USB and printing
  - If unsure of a request, please clarify
  - Provide documents as they are ready
  - Aim to provide all documents to inspectors by the morning of the final inspection day

Practical tips for inspections

Post inspection

- ***Inspection report and CAPA plan***
  - Provide any outstanding document requests to the inspectors as soon as possible – inspection report will be issued **4 weeks** from receipt of final document
  - Send the inspection report once received to the relevant persons/parties for response within **4 weeks**
  - You should have a method of recording and tracking your CAPA commitments
  - Inform us of any errors in the report with evidence – we will correct this in the final report
  - Contact us if you have an queries

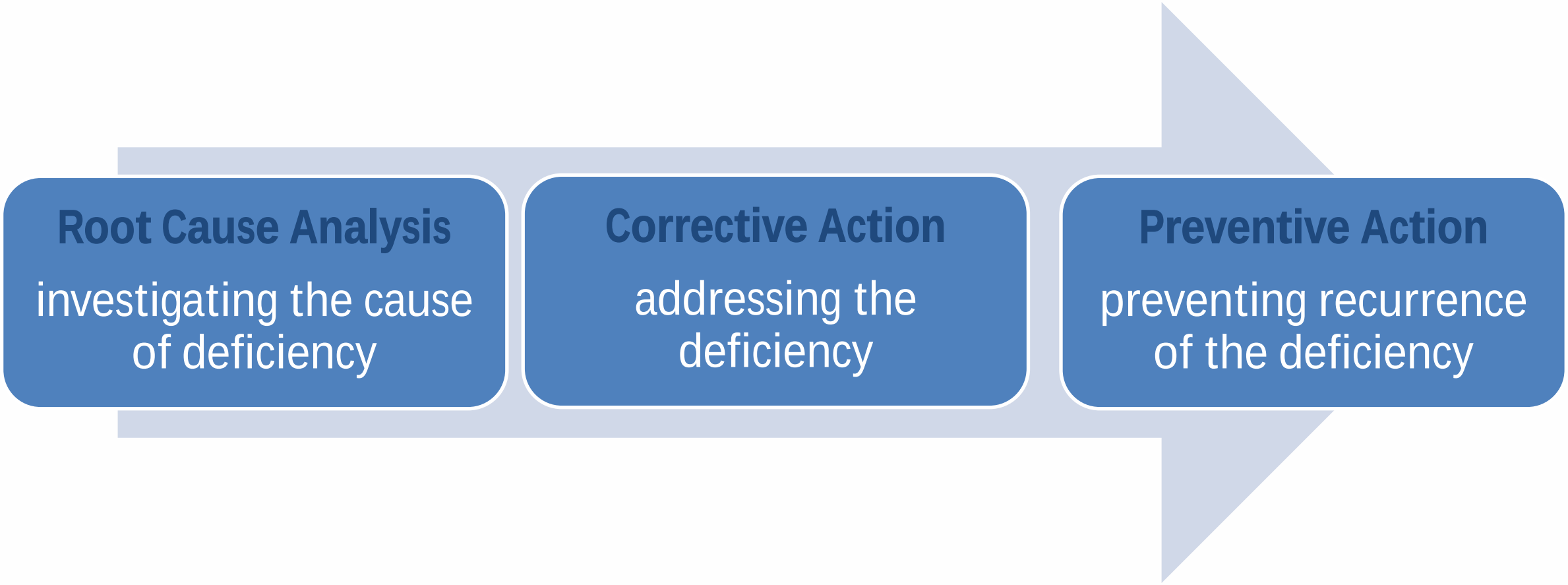
Summary

- Be organised and prepared
- Make sure staff are clear on their roles and responsibilities prior to, during and post inspection
- Maintain regular communication with the TGA
- Ask questions and provide feedback

Inspection experience

Workshop:
CAPA plan development

CAPA plan


Root Cause Analysis
investigating the cause of deficiency
Corrective Action
addressing the deficiency
Preventive Action
preventing recurrence of the deficiency

Developing a CAPA plan

- Consider:
  - **What** is the deficiency?
  - **Why** did it happen?
  - **Who** is responsible for the CAPA? Who is affected and who will implement it?
  - **How** should we address this deficiency and how do we prevent it from recurring?
- Be clear, specific and sufficiently descriptive in your response
- Be broad in your thinking and problem solving – reflect on the root cause and system as a whole
- Be reasonable with timelines for CAPA completion dates

CAPA workshop

- **What would be the recommended follow up/CAPA?**

TGA to complete	*Sponsor to complete*		*TGA to complete*	
Major deficiency	**Sponsor's response**	**Proposed completion date**	**Inspector's comments**	**Response accepted Y/N**
	Response date: Identified Root Cause of the deficiency: Proposed Corrective and Preventative action/s to the Root Cause: CAPA owner: Objective evidence provided:			

CAPA workshop

- Scenario 1: **Collection and collation of adverse drug reactions**
- Scenario 2: **Management of significant safety issues**
- Scenario 3: **Management of adverse drug reactions**
- Scenario 4: **Management of reference safety information**

Example of an acceptable CAPA plan

- **Deficiency: Case collection from partners and third party service providers**
  - There were delays in the receipt of adverse event reports from partners and service providers, resulting in late reporting of serious adverse reactions (>15 days) to the TGA
  - There were also adverse reaction cases identified that had not been appropriately forwarded to the sponsor and not reported to the TGA accordingly
  - The sponsor was not performing routine reconciliation of adverse event data with vendors to ensure the integrity of data transfer
  - To date, the sponsor has not audited any of their vendors or partners who perform pharmacovigilance activities for the company
  - The sponsor could not provide records of pharmacovigilance training of market research and patient support program staff undertaken before the date of program initiation and did not have adequate oversight of this

Example of an acceptable CAPA plan

- **Response date:** 27 March 2019

- **Identified Root Cause of the deficiency:**
  - The safety agreements in place (and current template) does not clearly state the responsibilities and timelines for reporting to sponsor and TGA if necessary (company process is to report any adverse reactions within 24 hours of receipt to the sponsor safety department, however this is not formalised in any documents)
  - The safety agreement does not include provisions for reconciliation
  - The sponsor has not audited any of their partners and third party service providers, however, they are able to at any time as stipulated in the safety agreement.
  - The safety agreement specifies that pharmacovigilance training is to be provided by the partner or vendor, however the sponsor does not request evidence of this.

Example of an acceptable CAPA plan

- **Proposed Corrective and Preventative action/s to the Root Cause:**
  - Serious adverse reaction case #12345AB and #98765CD, which had not been received by the sponsor, were reported to the TGA
  - Other non-serious adverse reaction cases were recorded into the GSD
  - The safety agreement template will be amended to clearly stipulate reporting responsibilities and timeframes (within 24 hours of receipt to sponsor), monthly reconciliation
  - The safety agreements will also be amended to require up to date pharmacovigilance training (upon employment and annually) and records to be held for inspection
  - New SOP will be developed describing the sponsor audit process of partners and vendors. The sponsor will undertake 6 monthly meetings to discuss the annual audit schedule. This will be risk-based and the scope of the audits will include reviewing pharmacovigilance training of staff.
  - A communication will be sent to all partners and vendors to notify them of the above process changes and obligations in the interim

Example of an acceptable CAPA plan

Proposed Corrective and Preventative action/s to the Root Cause (continued..):

- The sponsor will perform a reconciliation with their partners and vendors of the last 12 months (or from program start date) to ensure no adverse reports have been missed
- All partners and vendors have agreed to provide (re-)training to applicable staff to ensure staff training is up to date
- A tracker will be used by the partners and vendors to track adverse reaction reports and track receipt to sponsor by recording the GSD number

Objective evidence provided:

- Amended safety agreement template (pending) – due to be completed June 2019
- Annual Audit Schedule for 2019 (provided) – completed April 2019
- Records of staff training of partner and vendor staff (pending) – due to be completed June 2019

Questions

Contact us

- For PVIP-related questions:
  - pharmacovigilance.questions@health.gov.au
- For general pharmacovigilance questions:
  - pharmacovigilance.enquiries@health.gov.au

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