Workshop: Performing Detailed Investigations

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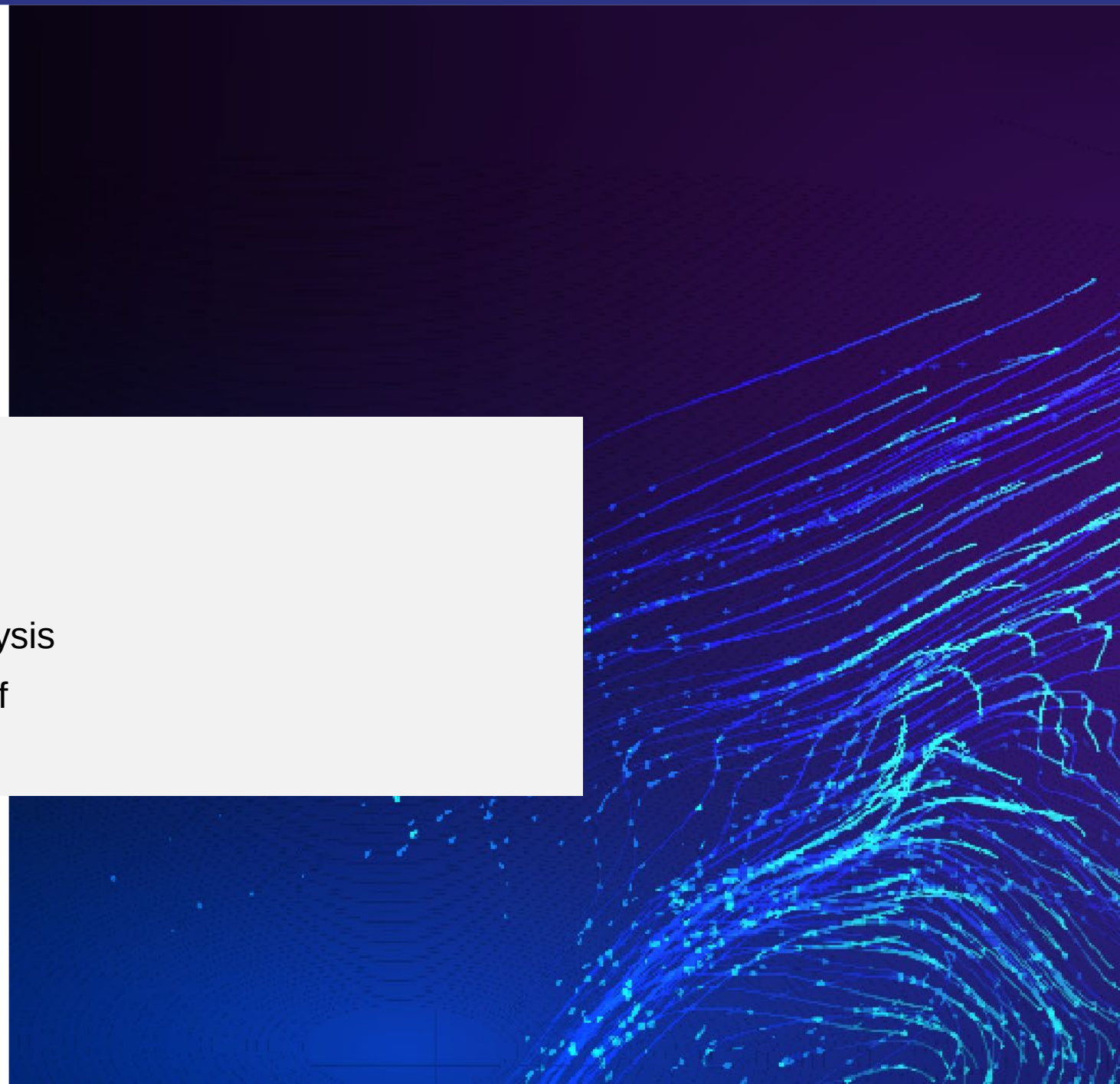
GMP FORUM 2024

Agenda

- Introduction
- Investigation overview
- Root cause analysis and examples
- Underlying principles for root cause analysis
- Group case study, discussion and debrief
- Conclusion



A common deficiency at GMP inspection

Poor investigations

Why?

- Timeliness
- The investigation doesn’t consider some factors
- Root cause analysis is not sufficient
- Investigation is not well documented
- Investigation is still not closed and product is released to market.
- Corrective and Preventative actions (CAPAs) not effective

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Mentions root cause analysis in investigations

1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

(xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems.

This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations.

The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles;

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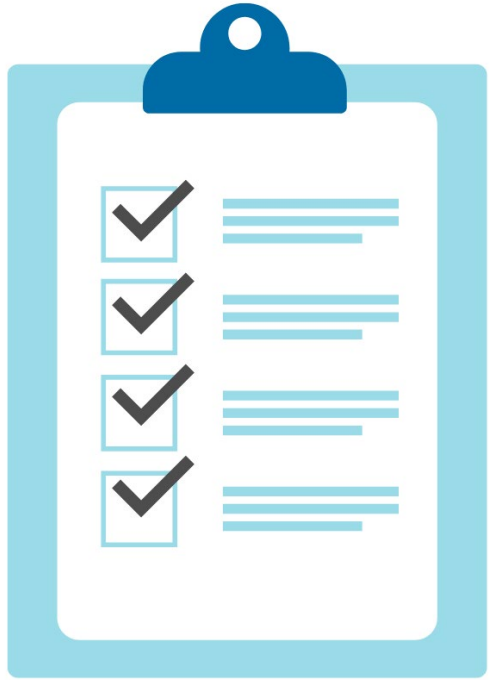
Mentions investigations and root cause analysis

1.8 Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

(*vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;*



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Mentions documenting investigations…

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

- *Investigations into deviations and non-conformances;*

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Quality risk management principles

1.12 Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.13 The principles of Quality Risk Management are that:

(i) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

(ii) The level of effort, formality and documentation of the Quality Risk Management process is commensurate with the level of risk.

Examples of the processes and applications of Quality Risk Management can be found inter alia in Annex 20 or ICHQ9.

Investigation process

7 steps to implement and document investigations.

Step 1: Describe the Event — Clearly And Concisely

Step 2: Collect Data

Step 3: Perform Root Cause Analysis (RCA)

Step 4: Perform Impact And Risk Assessments

Step 5: Determine CAPAs And Document Changes

Step 6: Form a Conclusion

Step 7: Initiate Effectiveness Checks (ECs)

Source: 7 Steps To Properly Navigate An Event Investigation (pharmaceuticalonline.com)

Root cause Analysis

What is root cause analysis?

The root cause analysis definition revolves around the process of identifying the source of a problem and looking for a solution in a way that the problem is treated at the root level.

PIC/S guide Annex 20 provides a number of risk management tools.

Root cause Analysis

An example – Root cause vs symptom

John is sick and has been throwing up at work, he’s going to a doctor to ask him to find the root cause of the issue he has.

For this example, we could just find a simple remedy for the symptom.

To stop throwing up at work, he might stay home to be in the bathroom.

But the solution only considers the symptom and does not consider the underlying cause of the symptom—causes like a stomach infection that requires medicine.

To solve or analyse a problem, we’ll need to perform a root cause analysis and find out exactly what the cause is and how to fix it.

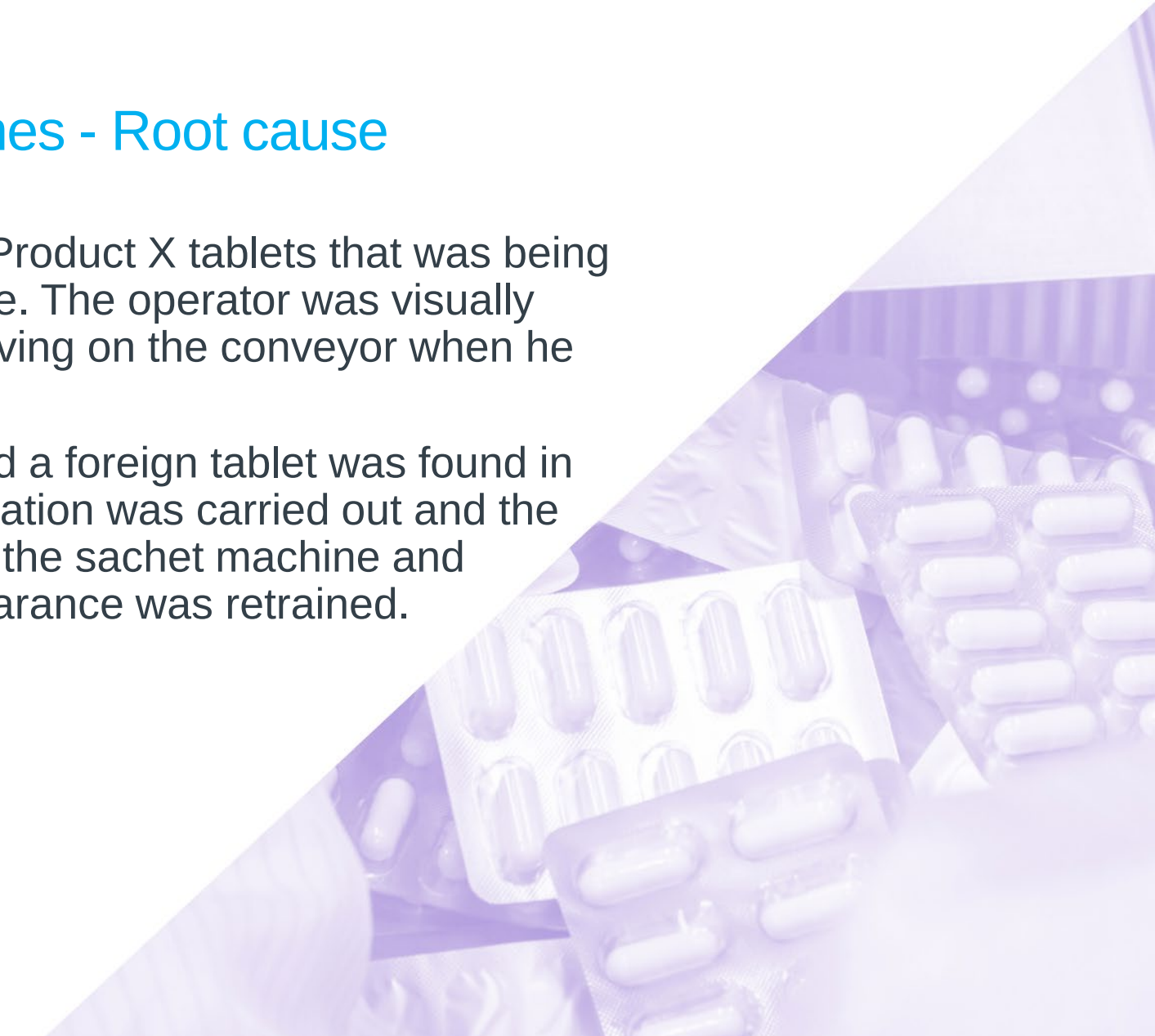
Root cause Analysis

An example - mix up of medicines - Root cause

A white tablet was found in a sachet of Product X tablets that was being packaged. Product X tablets were purple. The operator was visually inspecting the sachets as they were moving on the conveyor when he noticed the white tablet.

A deviation report was written that stated a foreign tablet was found in the sachet on the conveyor. An investigation was carried out and the root cause was a poor line clearance of the sachet machine and the operator who performed the line clearance was retrained.

Was this the root cause?



Root cause Analysis

Mix up of medicines – further considerations

The investigation considered a symptom which was the operator training.

There were also other things that needed to be considered to get to the root cause

The procedure was not adequate to perform an effective line clearance e.g. lots of spots in the machine where a tablet can get trapped.

Inconsistency in how the operators did the line clearance as the procedure was not clear on what to do and did not mention to strip the machine to ensure nothing foreign was in the machine.

The machine is not able to be stripped (only way to assure there are no tablets)and therefore not suitable…

Any other considerations?

Root cause Analysis

Some underlying principles

- Focus on correcting and remedying root causes rather than just symptoms.
- Don’t ignore the importance of treating symptoms for short term relief.
- Realise there can be, and often are, multiple root causes.
- Focus on HOW and WHY something happened, not WHO was responsible.
- Be methodical and find concrete cause-effect evidence to back up root cause claims.
- Provide enough information to inform a corrective course of action.
- Consider how a root cause can be prevented (or replicated) in the future.

Root cause Analysis

Case study for the session

- Work in groups
- Respond to the tasks
- Discussion/Debrief

Questions?

Scan this QR code with your device to submit a question

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Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration