Trending of Deviations/Performing Checks for Recurrence During Investigations

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Agenda

- Quality System Elements for Trending of Investigations
- Requirements for Effective Investigations & CAPA
- Performing Checks for Recurrence During Investigations
- Common Deficiencies Relating to Checks for Recurrence
- Summary and Key Points

Quality System Elements for Investigation Trending

- Annual Product Reviews.
- Management Review.
- Trending during Deviation/Laboratory/Complaint Investigations.

Annual Product Reviews

- EudraLex Volume 4, Chapter 1, Pharmaceutical Quality System, Paragraph 1.10:
  - (iii) A review of all batches that failed to meet established specification(s) and their investigation.
  - (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.
  - (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

Annual Product Reviews

- Trending of investigations in APRs:
  - Full listing of all investigations with short summary, classification & related CAPAs.
  - Overall trend in comparison to previous year.
  - Current numbers based on classification with comparison to previous year.
  - Trending based on system e.g. Manufacturing V Materials Management V Laboratory.
  - Trending based on root cause.
  - Identification of repeat (recurring) issues.
    - Assessment of associated CAPAs implemented.

Management Review

- EudraLex Volume 4, Chapter 1, Pharmaceutical Quality System, Principle & Paragraphs 1.5 & 1.6:
  - 'The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use'.
  - 'To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored'.
  - 'Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place'.
  - 'There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself'.

Management Review

- Trending of investigations during Management Review:
  - Number raised since previous review.
  - Number closed since previous review.
  - Number raised outside accepted timeline.
  - Number closed outside accepted timeline.
  - Aging of investigations not closed on time.
  - Investigations by Functional Area.
  - Trending based on root cause.
  - Number of confirmed recurring investigations:
    - Assessment of associated CAPAs implemented.

Performing Checks for Recurrence During Investigations

- Conducting thorough investigations including effective checks for recurrence as an integral part of the investigation process is key in supporting the Management Review process and in facilitating trending for inclusion in the Annual Product Review.

Checking for Recurrence During Investigations/Introduction

- All routine GMP inspections include a review of investigations relating to deviations, laboratory investigations and complaints.
- Lists of investigations requested in advance of the inspection.
- On review, recurring trends may be identified by inspectors.
- Level of oversight of such trends by the company is assessed during the inspection.
- Trending of such incidents by the company is not always thorough and robust.
- As a result, one of the most common deficiencies identified during GMP inspections is the absence of effective checks for recurrence being performed as part of deviation and complaint investigations.

What drives the requirement to check for recurring issues?

Chapter 1, EU Guide to Good Manufacturing Practice, Paragraph 1.4 (xiv) states the following:

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

- 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 preventative 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.

➢ The monitoring of CAPA Effectiveness requires that appropriate checks are performed to identify recurring issues.

Investigation Effectiveness

Goals of an Effective Investigation:

- Establish the true root cause/most likely root cause of the incident/issue.
- Based on root cause identify the most appropriate CAPA.
- Ensure CAPA is implemented in a timely manner to minimise future risk to product quality.
- Effectiveness of CAPAs implemented is verified based on pre-agreed criteria through the CAPA system.

On-going Confirmation of CAPA Effectiveness:

- Effectiveness of CAPAs implemented should also be monitored on an on-going basis.
- Performing thorough checks for recurring issues during investigations is a critical element of this on-going monitoring.
  - Challenges overall effectiveness of the investigation process.
  - Opportunity to challenge the appropriateness of CAPAs already implemented.
  - Opportunities for continuous improvement.

Overall Evidence from Inspections

- Most companies include a check for recurring issues within their investigation system.

- However, there can be a wide variation as to the standard of assessment and the level of documentation.

Most Common Deficiencies

- No definition or guidance as to what constitutes a recurring deviation and criteria for performing checks for recurrence are not clearly defined.
- Expectation:
  - Definition should be as broad as possible.
  - Not confined to product and batch:
    - Should consider other batches of same product.
    - Should consider other products as appropriate.
  - Should consider other manufacturing and packaging equipment as appropriate.
  - Should focus on the issue and the root cause.

Most Common Deficiencies

- Search Criteria are not adequately defined:
  - Appropriate search criteria may vary based on the type of incident in question.
  - The ability to perform the search will vary depending on whether there is an electronic QMS or only paper-based records.
  - The title assigned to the investigation is critically important in identifying recurring incidents.
  - Standardising terminology facilities effective recurrence checks.
    - In the case of potential contamination, this could be described in multiple ways. For example:
      - Contaminant found in Product A, Batch XXX.
      - Extraneous matter found in Product A, Batch XXX.
      - Foreign matter found in Product A, Batch XXX.
      - Unidentified material found in Product A, Batch XXX.
    - Will the companies search criteria identify the above as being potential recurrences?

Most Common Deficiencies

- No timeframe documented for performing checks for recurrence or timeframe inappropriate:
- Expectation:
  - Timeframe should be appropriate to the manufacturing volume of the product or the frequency at which the task/operation is being performed:
  - For example, for a high-volume product, a timeframe of 12 months may be appropriate. However, for a low volume product a longer timeframe of 2 to 3 years may be more appropriate.
  - Similarly, for a task that is being performed weekly, e.g sampling of the purified water system a timeframe of 12 months may be appropriate. However, for a task that is performed only monthly e.g environmental monitoring, a timeframe of 2 to 3 years may be more appropriate.
  - Similarly, if it relates to a cleaning failure, the timeframe should be appropriate to include a representative number of campaigns.

Most Common Deficiencies

- The check for recurrence is not documented in appropriate detail:
  - The ‘check’ can vary widely from a check box (Yes/No) to a detailed list of previous deviation numbers, descriptions and assessments of each.
  - In some cases, a list of deviation numbers is documented without a short description of each deviation.
  - In many cases there is no assessment of the incidents in question to justify whether or not they constitute a recurrent issue.
  - Expectation:
    - Previous incidents should be listed with investigation numbers and a short description.
    - There should be a brief documented assessment as to whether or not they represent a recurrent issue.

Most Common Deficiencies

- Recurrence checks were not performed for certain categorisation of investigations – e.g. 'minor' investigations.
  - Expectation is that there should be some assessment for recurrence for all investigations including minor investigations.
  - Level of rigour should be commensurate with the potential risk to product quality.
  - Not escalating recurring minor incidents could result in a failure to adequately address underlying issues which could later result in a more significant quality issue.
  - Expectation is that there are criteria documented as to when investigations are escalated to more significant level when multiple recurring incidents are identified.

Most Common Deficiencies

- There is no documented assessment as to whether the issue resulted from the same or different root cause.
  - The assessment of root cause is key to an effective assessment of recurrence.
  - Similar incidents which arise from different root causes are not true recurrences.
  - In any assessment of recurrence, confirmation of the same or different root cause is essential.

Most Common Deficiencies

- On occasions we find that similar issues are designated as ‘not true recurrences’ based on different root causes and this is not justified.
  - Examples of very similar incidents but root cause is worded slightly differently to justify why it is not a true recurrence.
- Companies are reminded that identification of recurring issues is not necessarily perceived as negative.
  - Accepting an error in relation to a previous investigation and taking appropriate action demonstrates a mature and effective quality management system.
  - Mistakes present an opportunity for learning and improvement of the process or system.
  - Continuous improvement is a key goal for all companies.

Most Common Deficiencies

- Frequently we find that following a confirmed recurrence, companies do not re-assess previous CAPAs implemented.
  - Failure to identify and implement the most appropriate CAPA?
  - Failure to implement CAPAs in a timely manner?
    - Caused by delayed implementation?
    - Original target date not appropriate and did not reflect the potential risk?
  - Reduces effectiveness of the investigation system and may ultimately put product at risk.
  - Where delays in implementing CAPAs result in further instances of the same issue this should be addressed as part of the investigation.

Compliant Investigations

- In the case of complaint investigations, due to time lags between implementation of CAPAs and the receipt of complaints from the market, it is possible that the event triggering the complaint predates the implementation of the relevant CAPA.

- Where relevant this should be documented within the investigation report.

Summary

- Performing checks for recurrence in an effective manner is an important element of the management of investigations.
- Clear guidance on how recurrence checks are to be performed should be available within the Quality System.
- Recurrence checks should be documented in appropriate detail.
- Identification of true root cause in all investigations is key.
- Identifying and implementing the most appropriate CAPA in a timely manner is critical.
- An assessment of previous CAPAs implemented should be conducted when a recurrence is confirmed.
- Effective recurrence checks during investigations facilitate trending for Management Review and for the Annual Product Review.

HPRA
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Thank You