Investigations Best Practices

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EXPERIENCE

- 30 years of pharmaceutical industry experience, including over 17 years at MHRA and over 20 years performing audits and inspections
- Former Head of the MHRA Inspectorate and Deputy Director, Inspection, Enforcement and Standards
- Led the creation of the risk-based inspection and compliance management principles at MHRA
- Former PIC/S Executive Bureau member and PIC/S lead assessor
- IRCA Principal Auditor PQMS - GMP Scheme
- Eligible Qualified Person since 2003, IMP batch release pre CTD
- 10 years at GSK, roles including Technology Transfer, Supplier Audits and R&D QA

AREA EXPERTISE

- GMP inspections of manufacturers of investigational drugs, finished drug products, active ingredients, excipients and packaging materials
- Regulatory risk-based inspection programs and approaches, including desk-based assessments
- New innovative technologies and processes; and associated regulatory thinking in these areas
- Developing training programs and conferences for international regulators and industry
- Regulatory crisis management (e.g. Pandemic, Heparin, drug shortages)

EDUCATION

- University of Hertfordshire, BSc (Hons) Chemistry with Chemical Technology, 1996
- University of Greenwich, MSc Pharmaceutical Science, 2002
- University of Warwick, MBA, 2022

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Why needed?

Why are good investigations needed

- This continues to be a regulatory hot topic
  - Previously covered at IPA in 2017 (MHRA/FDA)
- It is an area where significant regulatory observations continue to identified
- MHRA 2019 data:
  - Last data / pre-pandemic
  - Top 2 inspection findings made were related to this subject
  - This contributed to over 300 regulatory findings of which 10 were critical findings

MHRA 2019 data – No. 1 deficiency cited

- **Chapter 1 Pharmaceutical Quality System C1.4(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 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

Ref EU GMP

MHRA 2019 data – No. 2 deficiency cited

- **Chapter 1 Pharmaceutical Quality System C1.8(vii)**
  - Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented

Ref EU GMP

Issues seen

System issues identified by Regulators

- A strong principle of GMP is operating in a state of control.
  - The PQS is the foundation which helps companies achieve this state.
  - During inspection, Regulators will look for evidence that the investigation and Corrective and Preventive Action (CAPA) system is operating in a state of control.
- There are some symptoms if it is not, these can include:
  - investigations being raised long after the event occurred or taking an unreasonable time to complete
  - root cause analysis being raised as a CAPA to enable premature deviation closeout
  - a large proportion of CAPAs being overdue or being extended
  - human error being listed as a frequent root cause
- In view of the requirement to continually improve and perform appropriate root cause analysis, regularly recurring issues are an indicator that the system is ineffective.

Investigation issues identified by Regulators

- Assumption rather than an evidence-based investigation
  - Being led by previous experience to draw conclusions
  - Assumptions that procedures and methods are robust
  - Human error incorrectly assigned
- Risk assessments being used to justify taking, or not taking, certain actions
  - Arguments used to support course of action taken
  - May downplay true level of risk
  - Risk assessment needs to be appropriate

Best practices

Best practices

- Effective investigations
- Risk assessments
- Consideration of patient safety
- Root cause analysis
- Targeted CAPAs
- A well-managed system

Effective investigations

- Investigations should be launched from the outset with the intention of establishing true root cause and identifying appropriate CAPAs.
- It is not only a mechanism to protect patient safety, but a way to improve the efficiency of an organisation’s operations
- Investigators should consider beyond the initial probable root cause of an incident and confirm or rule out other plausible potential root causes. This should include speaking to relevant colleagues involved in the incident and best practice would include visiting the areas involved.
- A review of previous incidents is important to identify if this is a recurring issue within that area, on a specific piece of equipment, or a process

Risk assessments

- Risk assessment on the batch, campaign and previous campaigns should be considered as appropriate.
- Guidance on risk assessment methodology is available in ICH Q9
  - Under revision to improve areas of current QRM application, including *High levels of subjectivity in risk assessment and in QRM outputs*
- The assessments should be sufficiently detailed to cover all reasonable risks, be evidence-led and drive decisions on batch disposition and/or recalls, rather than building cases to support any decisions already made.
- Some issues can appear minor at surface level, only when assessed will more significant risks become known.
- The extent of the issue and other batches affected should be considered, it may be that the issue has been there but undetected for some time.

Consideration of patient safety

- The quality, safety and efficacy risk in the context of the patient should be central to all investigations
- It should be clearly considered and included in the associated documentation
- Thought must be given to other circumstances in which the failure may not have been detected and what that risk profile could be

Root Cause Analysis

- There are several approaches to root cause analysis that are well known and recommended, however, Regulators report that they do not always see them used - even when there are clear advantages or 'true root cause could not be identified' has been recorded in the report
- Such approaches include:
  - Ishikawa fishbone diagrams
  - Kepner-Tregoe
  - '5 whys' / 5W2H
  - Thinking wider and considering PQS trend data and any potential links.
- Examples of going wrong……..
  - Equipment breakdown
  - Spider in production

Targeted CAPAs

- Effective root cause analysis will lead to the identification of appropriate and relevant CAPAs.
- These should:
  - be clearly defined
  - directly address the root cause
  - have realistic and risk-based target dates
  - be monitored to conclusion
  - have effectiveness checks
- Consider the impact of target completion dates.
  - think about the application of arbitrary completion times – are they too optimistic?
  - have CAPAs that should be implemented urgently or before manufacture of the next batch have been identified.

A well-managed system

- The systems supporting investigation activities and outputs should be monitored with trending to obtain meaningful information that can be used to drive routine improvements and ensure that approved timescales are met
- This includes scrutiny during management review and escalation where needed to ensure the system remains in control and an effective means of protecting patients when things have gone wrong
- But be mindful of metrics driving unintended consequences
- Get out and see the areas – Gemba
- Future trends
  - Use of technology to support systems

Metrics: careful selection

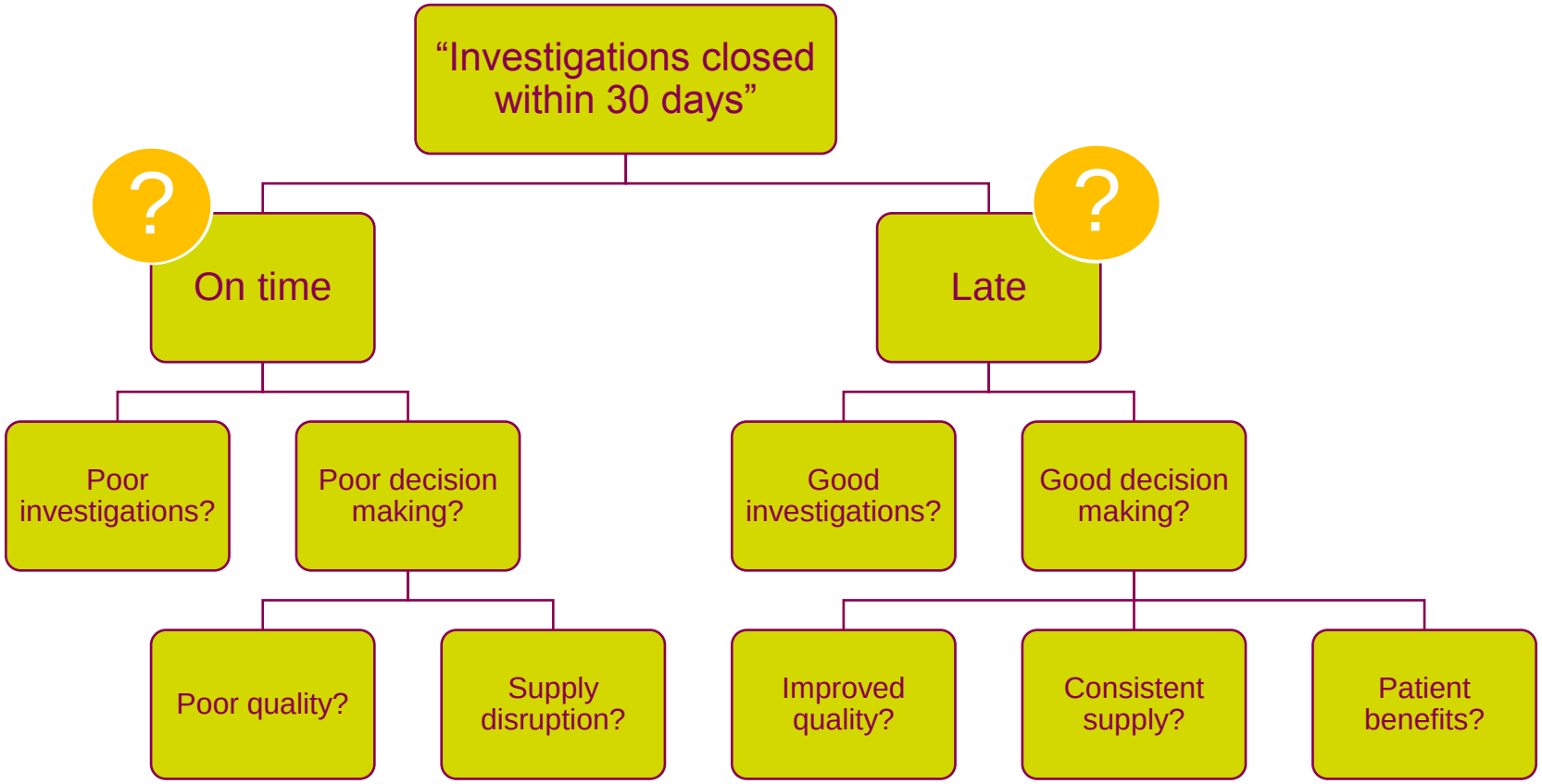
- Careful selection of metrics is required
  - What behaviours do the metrics demonstrate?
  - What behaviours do the metrics influence?
  - What is the relevance of each metric to product quality or patient safety?

“The only true measures of quality are the outcomes that matter to patients”

Michael E. Porter and Thomas H. Lee, MD

Harvard Business review October 2013

The importance of context



Gemba

- Drives continuous improvement
  - Shop floor problem solving with those that experience them
- Supports identifying issues
  - Quality risks
  - Waste
  - Root causes
- Makes leaders visible
- Learn from the shop floor

Conclusion

Investigations Best Practices

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- Risk assessments
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Acknowledgements: MHRA blog, IPA 2017 (Birse/Mozzachio), IPA 2018 (Birse)

Thank you