QUOTIENT BIORESEARCH

Use of a CAPA System in Handling Anomalous Results

With a Focus on Maintaining GCP Compliance

Answers Through Innovation

Anomalous Results

- Handled per SOP
  "Unexpected Events in Regulated Bioanalysis Studies"
- Any occurrence that falls outside routine situations encountered and which may warrant further investigation
- Decision on whether to investigate made by SD/PI/APM
- Decision on whether to halt the study made by SD/PI/APM
- Outcome of investigation approved by SD/PI/APM and facility management
- Documentation is via a CAPA system

Corrective And Preventative Action (CAPA)

Corrective Action

To eliminate any cause for non-conformities to prevent them happening again

REACTIVE

Preventative Action

To eliminate any potential cause for non-conformities to prevent them happening in the future

PROACTIVE

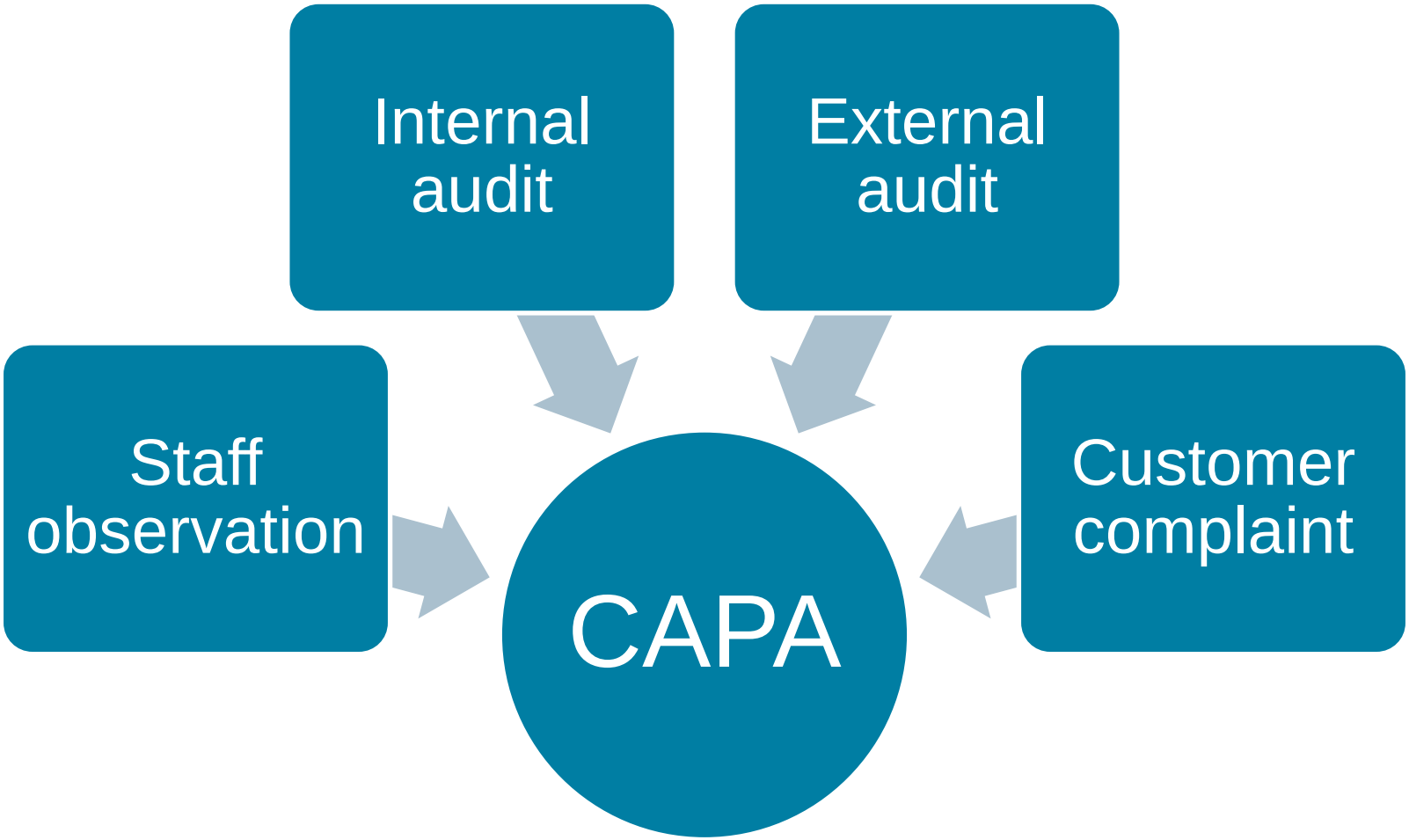
Corrective And Preventative Action (CAPA)

- ISO 9001 & 17025 Standard requirement

  "8.5.1 Continual improvement
  The organisation shall continually improve the effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, ***corrective and preventative actions*** *and management review."*

- Quality Assurance department are responsible for
  - assigning actions to individuals
  - following up progress on actions
  - ensuring CAPAs are closed out

Source of CAPA Items



UK Perspective

BARQA
Good Clinical Laboratory Practice
2003, Tim Stiles & Vanessa Grant

The Medicines for Human Use (Clinical Trials) Regulations
2004

MHRA
Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples
2009

Quotient Bioresearch Experience

- We have conducted clinical Bioanalysis to GCP since 2004
- First MHRA standalone GCP inspection March 2010
- Combined GLP/GCP inspection in February 2011
- Focus on
  - Contracts and agreements
  - Requests for extra analyses
  - QC of clinical trial kits
  - Receipt of unexpected samples
  - Sample label information
  - Policy for reporting serious breaches
  - Staff training

Recent EMA Guideline

Guideline on bioanalytical method validation
(EMEA/CHMP/EWP/192217/2009)

"The validation of bioanalytical methods and the analysis of study samples for clinical trials in humans should be performed following the principles of Good Clinical Practice (GCP). "

EMA Reflection Paper

Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples
(EMA/INS/GCP/532137/2010)

"…anomalous results or unexpected values associated with pharmacokinetic analysis may indicate incorrect dosing or marked differences in a subject's ability to metabolise an investigational medicinal product which may potentially have safety implications."

"The most effective quality assurance programmes will include a documented CAPA procedure "

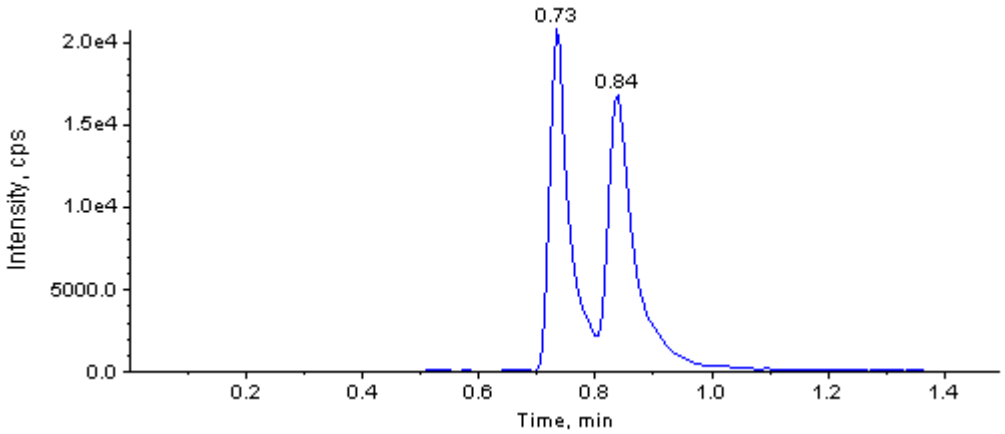
Unexpected Events in GCP Studies

Unexpected results	Deviations from protocol	Inappropriate labelling
Unexpected samples received	Requests for extra tests	Unblinding

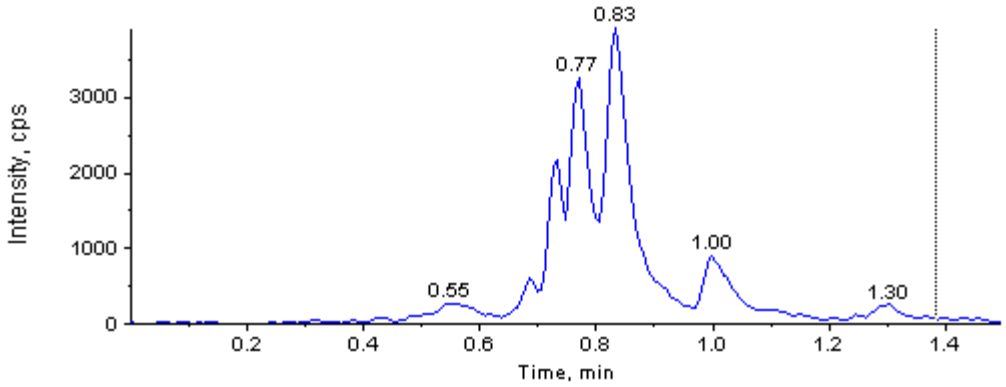
Real Example 1 - Mis-Dosing

- SAD study
- Subject X dosed active → all results BLQ
- Subject Y dosed placebo → all results quantifiable
- Investigated possible sample mix-up in our lab
- Re-analysed samples and confirmed results
- Potential serious breach reported to MHRA
- Cause identified = different blinding codes sent to CMO and bioanalytical lab

Real Example 2 – Unexpected Metabolites



STD 4



Subject sample

Summary

- Must consider wider context of unexpected events, rather than focus on anomalous results
- Unexpected events can be a compliance issue in a GCP setting
- A CAPA system cannot replace scientific expertise but can be a useful tool in managing investigations

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