Filter Integrity Test fault handling - GMP view

Contents:

- GMP requirements
- Pre and Post Use Integrity Testing
- Impact of new EU GMP Annex 1 requirements
- Fault handling

GMP requirements

- Already covered

- The main concern is that the filter, located in its housing, has performed its job correctly and that the material being filtered is free from microorganisms until point of use

PUPSIP

- The DRAFT version of Annex 1 introduces a formal integrity test of sterile filters prior to use
- Current version:
  - *"The integrity of the sterilised filter should be **verified** before use and should be **confirmed** immediately after use ... " (Annex 1 – Clause 113)*

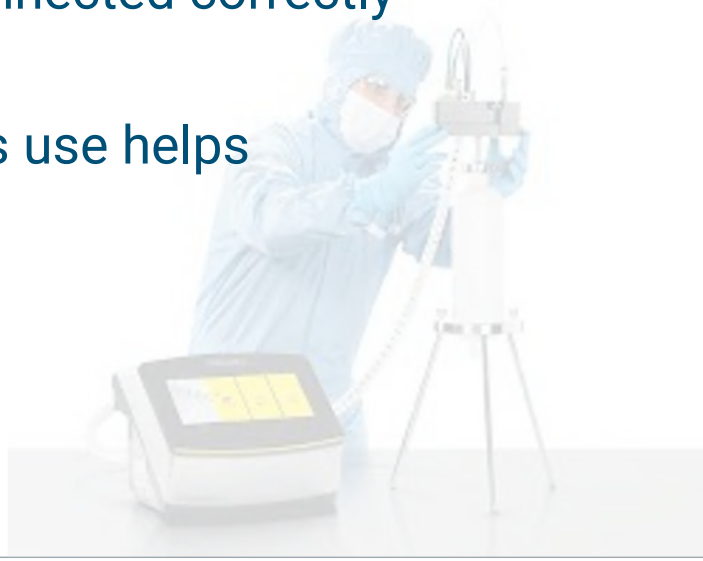
- **Pre Use Post Sterilisation Integrity Test**

PUPSIP

- The DRAFT version of Annex 1 introduces a formal integrity test of sterile filters prior to use
- DRAFT version:
  - *"The integrity of the sterilized filter assembly should be **verified by testing before use**, in case of damage and loss of integrity caused by processing, and should be **verified by on line testing immediately after use** by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test. It is recognised that for **small batch sizes**, this may not be possible; in these cases an **alternative approach** may be taken as long as a formal risk assessment has been performed and compliance is achieved. There should be written integrity test methods, including **acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated**. Results of the integrity tests (including failed and repeated tests) should be included in the batch record ... " (Clause 8.84)*

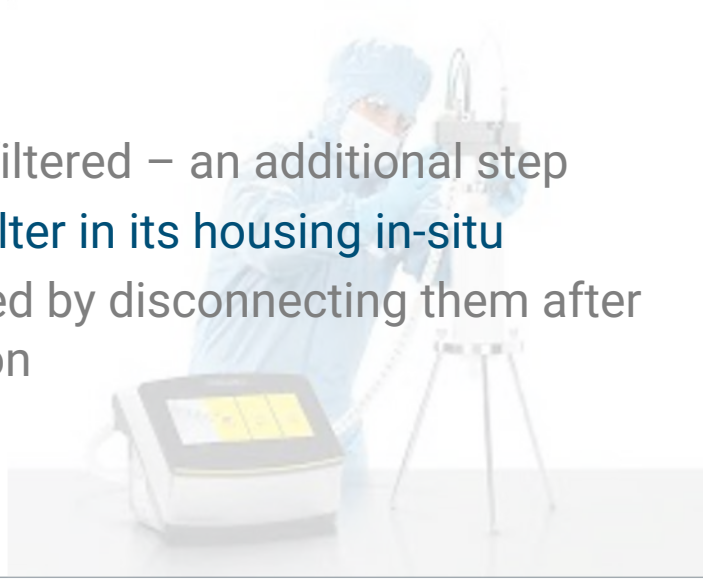
PUPSIP

- Background:
  - Filter may have a hole in it that is plugged as part of the filtration process
  - May then pass a post-use integrity test, but batch is not sterile
  - Filter may become damaged by the sterilisation process
  - Filter may not be sitting in its housing or connected correctly
  - Integrity testing the filter before and after its use helps increase sterility assurance



PUPSIP

- Issues:
  - To Integrity Test a filter it needs to be wet
    - Immediate problem for gas filters as these will then need to be dried
  - Option to wet the filter – **product**
    - Loss of product as part of the wetting process
  - Option to wet the filter – **water**
    - An additional step
    - Dilution of the product
    - What do you do with the water that you have filtered – an additional step
  - You need to have the ability to Integrity Test the filter in its housing in-situ
    - Often the filter and housing are Integrity Tested by disconnecting them after use and taking them to a Integrity Test location



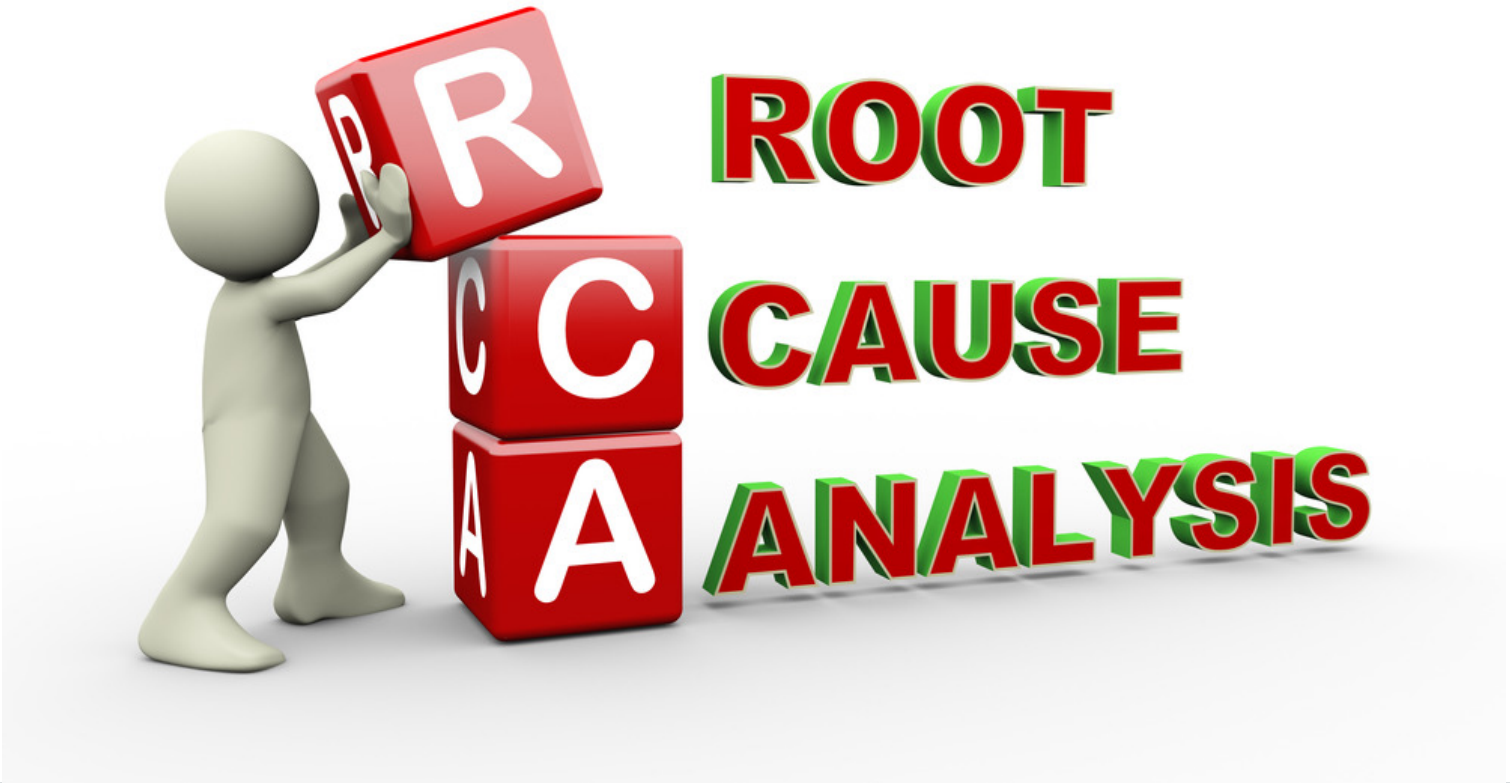
Fault handling

- It is possible to make an integrity test result invalid
- Typical examples:
  - Integrity test equipment fails
  - Correct pressures not achieved
  - Test not set-up correctly
  - Operator error
- There needs to be a formal system to investigate such failures
  - Similar approach to dealing with Out Of Specification results in the laboratory
- Failures need to be recorded in the batch record
  - Along with any supplier certificates and print-outs

Fault handling

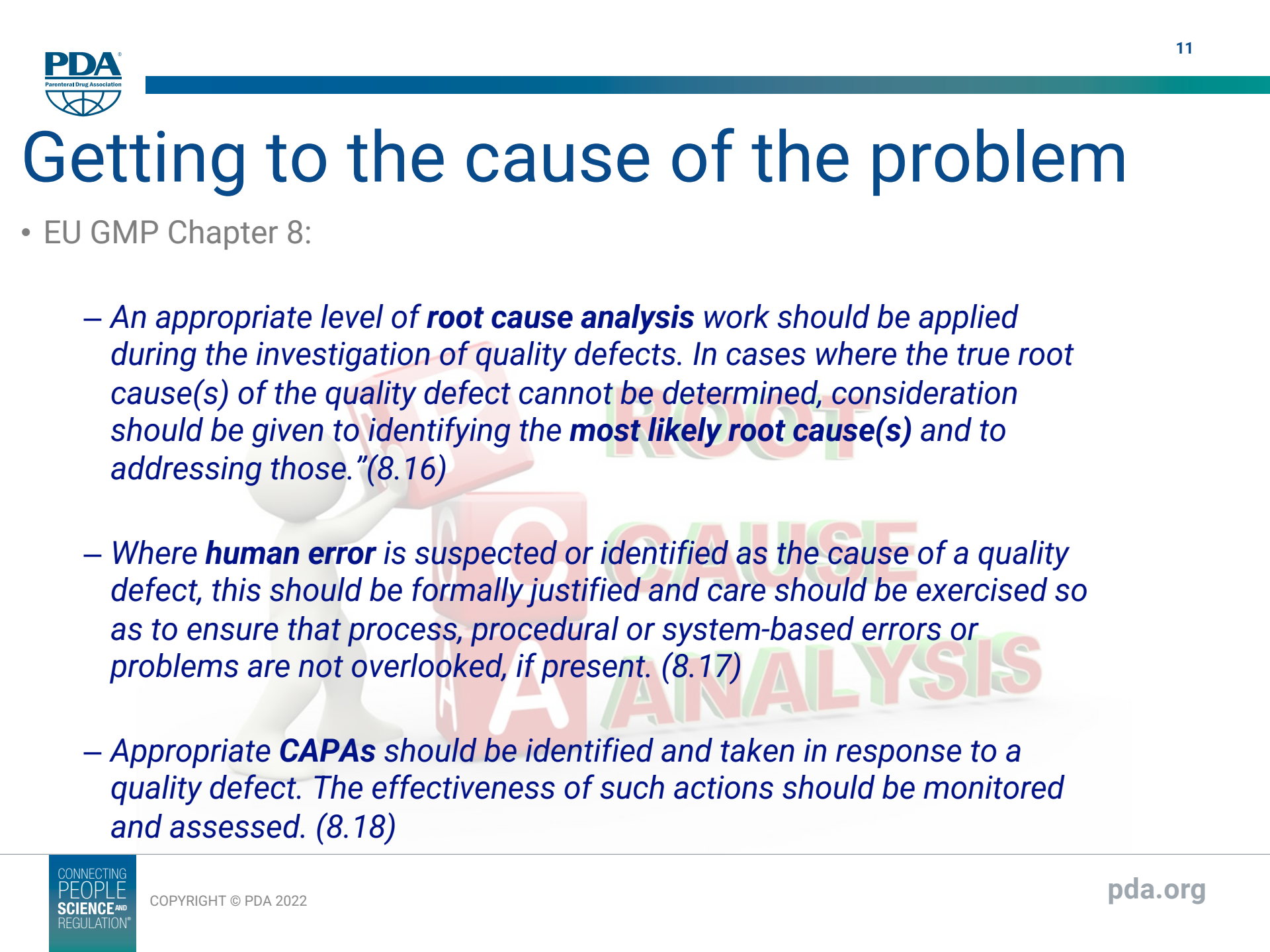
- In the event of a true failure then the equipment and (unless enclosed) the area, need to be viewed as contaminated
  - Re-cleaned, sanitised and sterilised as necessary
- Consideration needs to be given to other products and other batches, especially if the filter is in use for more than one batch
  - Failures of gas/ vent filters

Getting to the cause of the problem

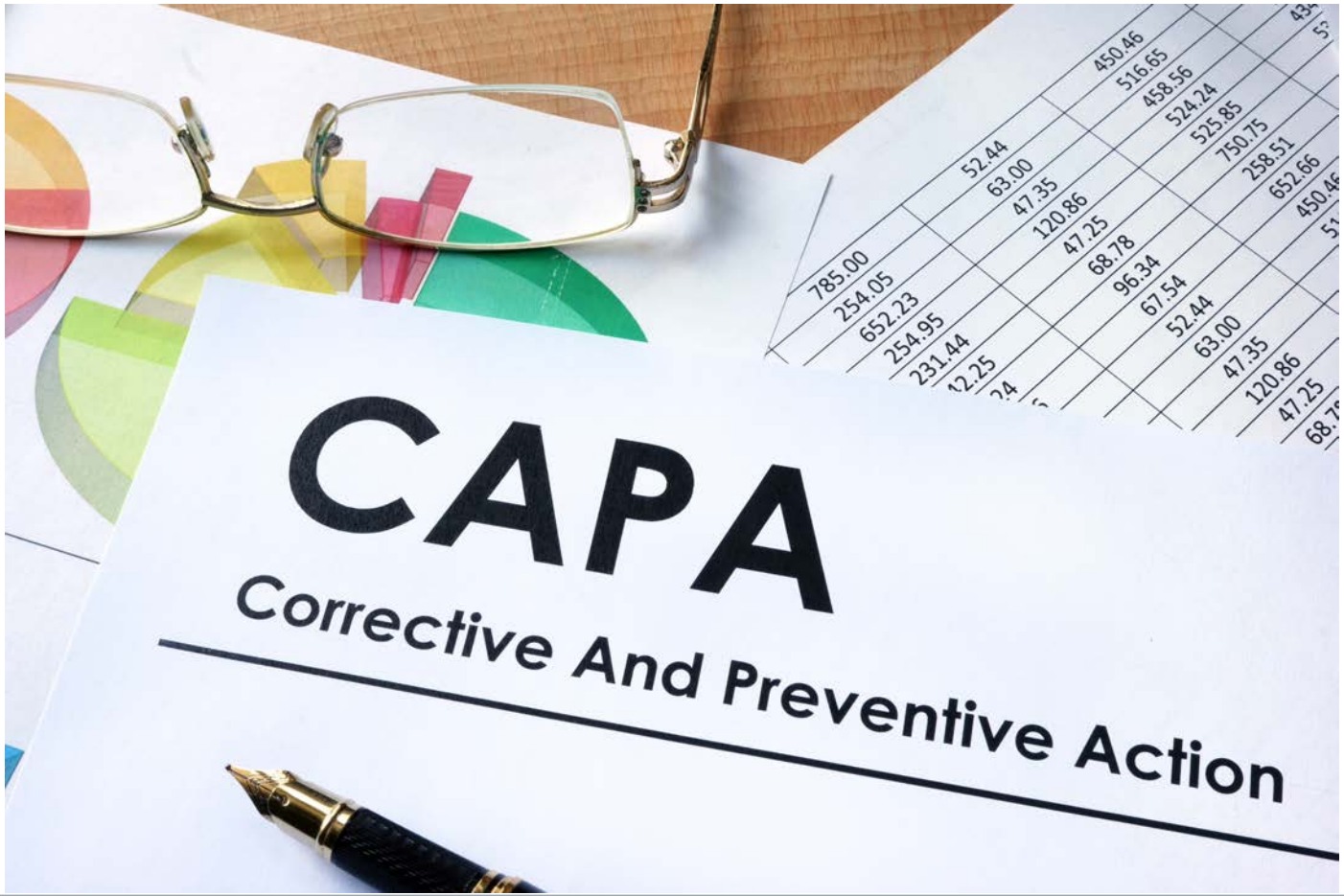


Getting to the cause of the problem

- EU GMP Chapter 8:
  - *An appropriate level of **root cause analysis** work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the **most likely root cause(s)** and to addressing those."(8.16)*
  - *Where **human error** is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present. (8.17)*
  - *Appropriate **CAPAs** should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed. (8.18)*

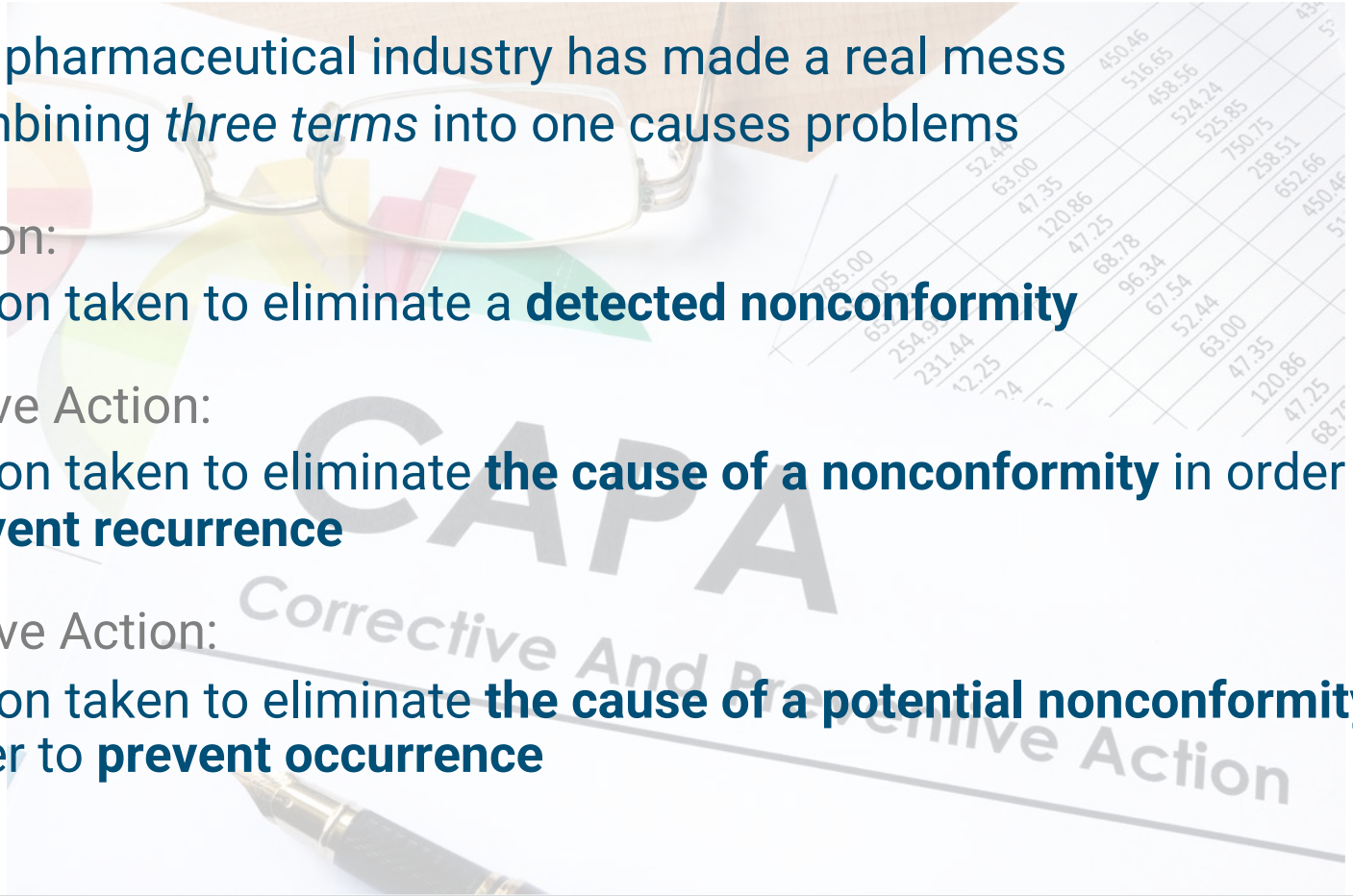


C, CA & PA (ISO 9001)



C, CA & PA (ISO 9001)

- CAPAs
  - The pharmaceutical industry has made a real mess
  - Combining *three terms* into one causes problems
- Correction:
  - Action taken to eliminate a **detected nonconformity**
- Corrective Action:
  - Action taken to eliminate **the cause of a nonconformity** in order to **prevent recurrence**
- Preventive Action:
  - Action taken to eliminate **the cause of a potential nonconformity** in order to **prevent occurrence**



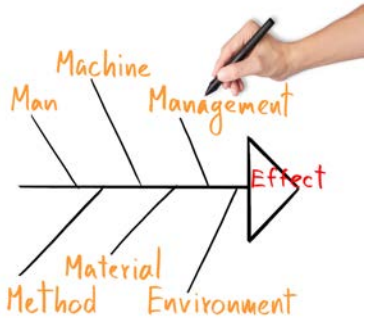
Getting to the cause of the problem

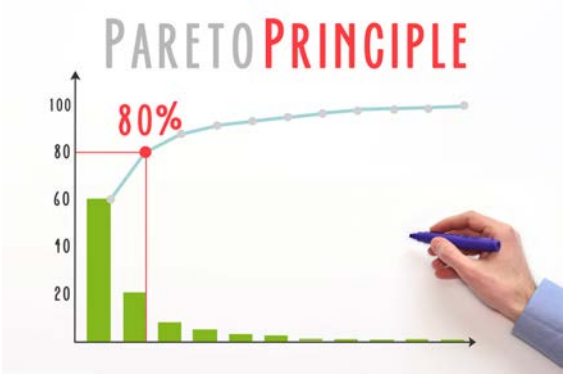
- Avoid simply blaming the individual
  - GMP states to be **very careful** about doing this

- Establishing what the problem is in the first place
  - The scale, impact and cause of the problem needs to be determined
    - *Root Cause Analysis* now a specific GMP requirement

Getting to the cause of the problem

- Problem solving tools
  - –Brainstorming
  - –Cause and Effect
  - –Pareto analysis
  - –5 Whys





References

- EU GMP Directives and Guidelines:
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- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice

- ISO 9001
- https://www.iso.org/iso-9001-quality-management.html