# Lecture 4: Pharmaceutical Quality System

Thomas Krieger, Ph.D., KRIEGER Unternehmensberatung - Pharma

# Definitions

**Correction**
**Corrective Action (QA)**
**Preventive Action (PA)**
**Effectiveness Check (EC)**

What are effective CAPAs?

How can I predict effectiveness?

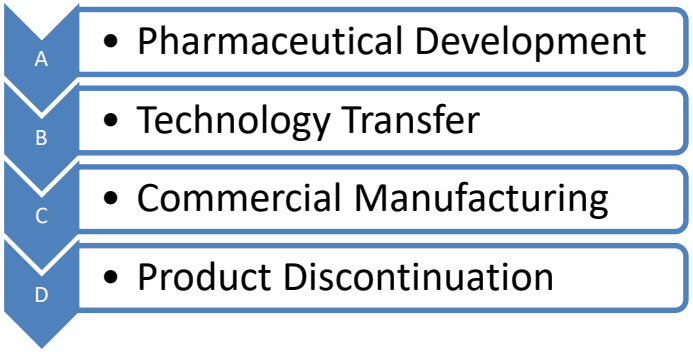
How can I measure and proof effectiveness?

# Pharmaceutical Quality System (PQS)

Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

"ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management"."

"Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle.":



## Pharmaceutical Quality System Elements

The elements described below might be, required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality.

1. Process performance and product quality monitoring system
2. Corrective action and preventive action (CAPA) system
3. Change management system
4. Management review of process performance and product quality

# ICH Q10 PHARMACEUTICAL QUALITY SYSTEM

## 3.2.2 Corrective Action and Preventive Action (CAPA) System

The pharmaceutical company should have a **system for implementing corrective actions and preventive actions** resulting from the investigation **of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends** from process performance and product quality monitoring.

A **structured approach to the investigation** process should be used with the objective of determining the root cause.

The **level of effort, formality, and documentation** of the investigation should be commensurate with the level of risk, in line with ICH Q9.

CAPA methodology should result in **product and process improvements** and **enhanced product and process understanding**.

# Action and Correction – Some definitions

## Correction:

Actions that correct a detected non-conformity, the impact of the incident, e.g. by rework. (ICH Q10, ISO 9000:2005)

## Corrective Action (CA):

Action to eliminate **the cause** of a **detected non-conformity** or other undesirable situation. NOTE: Corrective action is taken to **prevent recurrence** whereas preventive action is taken to prevent occurrence. (ICH Q10, ISO 9000:2005)

## Preventive Action (PA):

Action to eliminate **the cause** of a **potential non-conformity** or other undesirable potential situation. NOTE: Preventive action is taken to **prevent occurrence** whereas corrective action is taken to prevent recurrence. (ICH Q10, ISO 9000:2005)

## Immediate Action:

Actions that are immediately (in a temporal sense) taken for correction or as corrective or preventive action. (not a regulatory definition)

## FDA: Purpose of the Corrective and Preventive Action System

- To collect and analyze information to **identify actual and potential** product and quality problems
- To **investigate product and quality problems** and take appropriate and effective corrective or preventive action
- To **verify or validate the effectiveness** of corrective and preventive actions

## One day in the warehouse …

**Situation / Background:**

The central control system reported an high temperature alert at one refrigerator that is being used for storage of a cold chain product.

The technician checked the situation on the spot and found the door of the refrigerator open.

**Actions taken:**

- The technician transferred the packages of the product from the refrigerator with the alert to another refrigerator having the correct temperature.
- The technician closes the refrigerator's door.
- Temperature recordings of the refrigerator and stability data were reviewed in order to assess any impact on the product.
- The technician detected that the refrigerator stands inclined on the floor to enable the door to open by itself. He corrected the vertical position of the fridge.
- The technician affixed a lock on the refrigerator's door.
- The technician checked all refrigerators and affixed locks on the doors of each refrigerator.

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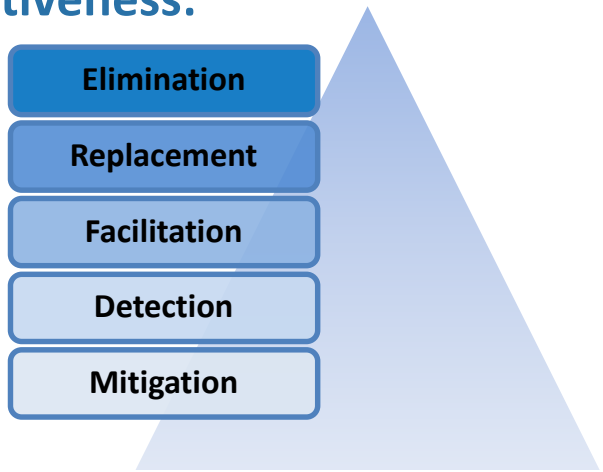
| CA | • The technician affixed a lock on the refrigerator's door. |
| PA | • The technician checked all refrigerators and affixed locks on the doors of each refrigerator. |

## Strategy for CAPA definition

- The ideal corrective action is to make a fundamental change that prevents the failure from ever happening again.
- Some corrective actions are more effective than others.
- PREVENTION is the KEY!

### Strategies in order of decreasing effectiveness:



# ELIMINATION

Eliminate the ***possibility*** of error. This can be accomplished by eliminating the task.

Examples

- Eliminate mixing errors by purchasing pre-mixed materials.
- Eliminate transport of intermediates between production and warehouse

Elimination can also be accomplished by a **poka-yoke** (an error-proof device).

Examples

- Release for use by Barcode- or RFID-Scan (weighing center, packaging)
- Pick-by-Light-Technology (order picking in the commissioning department)
- Cash machines release money only after removal of the credit card
- Alignment of SIM-Cards in mobile phones
- Different diameters of fuel nozzels

# Replacement

Change the current process by replacing it with one that is more reliable.

Examples

- Install bar-code scanners to replace 4-eyes-principles.
- Replace human inspection with automated 100% inspection
- Replace manually recording by linking the measurement device to a printer.
- Install mechanical limiting devices or PLC programs so that a process cannot exceed a specified range.
- Add redundant sensors on machines so if one sensor fails, the other will still work and the process is still OK.

## Facilitation

Make the process easier to perform by using “Visual Factory” techniques such as 5-S and color coding. Make errors more obvious.

Examples

- Use dedicated storage areas to reduce the possibility of mix-ups.
- Reduce material handling.
  Each movement is an opportunity for a mistake.
- Add pictures to procedures for illustration.

# Detection

Improve detection by adding new or better sensors. Do this at the source if possible. Understand that a corrective action that improves detection is inherently weaker than a corrective action that eliminates the problem.
Why? Because detection does not prevent defects, it just prevents escapes.

Examples

- Add audible alarms or lights if a process is out of tolerance.
  Better yet, automatically shut down, or add an interlock so the process cannot move to the next step.
- Add tick-boxes and grey fields in record documents to guide the user and support him to detect missing actions and recordings.

# Mitigation

Minimize the effect of the error. This is the weakest form of corrective action.
For most companies, your product designs are constrained.
Probably the only way to mitigate is to sort or rework.

Examples

- Sort and/or Rework should be viewed as a crutch / an interim step only, not a permanent corrective action.
  This is true even if you design a perfect automated re-inspection system.
- Sometimes you can combine detection and mitigation.
  Example: install a metal detector with a link to the conveyor. When metal is detected, mitigate by stopping the conveyor before e.g. contaminating the bin.

## Effectiveness Check (EC) ✓

- If corrective or preventive actions have been taken, effectiveness has to be adequately checked and proofed.
- Suitable ECs are measurable and reveal unambiguous results.
- Actions and Effectiveness Checks might have been completed already during investigation, e.g.
- CA: like-by-like exchange of a heat detector ➔EC: calibration passed
- In case, several actions have been defined, it is often impossible to define individual checks for each action ➔ Define comprehensive ECs.
- A negative result of an effectiveness check requires a new investigation and new CAPAs.

## Examples

### Active checks

Supervision of the next three process performances,
e.g. of the filling operator.

### Passive checks

Review recurrence or occurrence after a certain period of time
(e.g. 6 months after implementation).

**Active checks should be preferred instead of passive checks wherever possible!**