'CAPA' Refer to / taken from Ensuring Compliance: Navigating the EU MDR for Drug-Device Combination Products

**This item addresses Corrective and Preventive Action (ISO 13485:2016 §8.5.2 and 8.5.3) and requirements for associated statistical analysis (ISO 13485:2016 §7.3.6, §7.3.7, §7.5.6, §8.1 and §8.4)**

## A. QMS Requirements

### 1. EU Requirements

**EU medicinal product Directive 2001/83/EC** has the requirements for Single Integral DDC to comply with GSPR Annex I of MDR 2017/745 (Article 117). There is therefore no requirement to comply with EU MDR 2017/745 Article 10 General obligations of a manufacturer:
(l) management of corrective and preventive actions and verification of their effectiveness.
However, **ICH Q10, section 3.2.2** "*Corrective and Preventive Action (CAPA) System*" have requirements that apply to Single Integral DDC product.

### 2. US Requirements

**Under US 21 CFR §4A regulation and guidelines**, if the combination product include a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug **cGMPs**, the following provisions of the QMS regulation must also be shown to have been satisfied:

- 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §8.5.2 Corrective action and §8.5.3 Corrective action

**Similarities and differences**
**Similarities**
No significant difference when considering the 21 CFR 820.10 as to CAPA and ICH Q10. ICH Guideline and US requirements for QMS are similar in procedural requirements and records for Corrective and Preventive action.

**Differences**
Small differences lie in the following points:

**1. The use of statistical analysis**

- 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §7.3.6 D&D verification, §7.3.7 D&D validation, §7.5.6 Validation of processes for production and service provision, §8 (Measurement, analysis and improvement) - §8.1 General and §8.4 Analysis of data, all underline the need to use statistical methodology.

- ICHQ10 underlines the need to use statistical analysis to understand product or process variability only.

**The preferred steps you can take to address these differences**
Integrate both approaches by using statistical methods to meet the broader requirements of 21 CFR 820.10 various paragraphs incorporated from Requirements for a quality management system from the ISO 13485:2016 (including design and development verification, validation, and process control) while also focusing on understanding variability as emphasized by ICH Q10.

## 2. The quality system

- US21 CFR 810.10 §8.5.2 Corrective action and §8.5.2 Corrective action underline the need to investigate root cause that might affect product, manufacturing process but also the quality system applicable to medical devices.
- ICH Q10 stays more general when requiring that a structured approach should be used to determine the root cause and refers explicitly to product and process impacts.

**The preferred steps** you can take to address these differences:
Implement a Structured Approach by (1) using root cause analysis (RCA) tools such as the 5 Whys, Fishbone Diagram, Pareto Chart, Fault Tree Analysis and Failure Mode and Effects Analysis (FMEA) and (2) ensuring that the RCA process is thorough and systematic, addressing all potential areas of impact.

- 21 CFR Part 820.10 §8.5.2 Corrective action and §8.5.3 Preventive action imply that the CAPA information are disseminated to all those who are directly responsible for assuring the product quality. Furthermore, pertinent information related to CAPA is input for management review.
- ICH Q10 specifies that the level of effort, formality and documentation of the investigation should be commensurate to the risk as per ICH Q9.

**The preferred step** you can take to address these differences:
Develop or update the SOPs to reflect the **integration of both ISO 13485 CAPA processes and ICH Q10**. Include specific sections that address the communication and documentation requirements of 21 CFR 820.10 and the risk-based approach of ICH Q10.

## B. Background on CAPA

CAPA is crucial for identifying and addressing issues, preventing recurrence, promoting continuous improvement, ensuring regulatory compliance, managing risks, providing documented evidence, enhancing customer satisfaction, and promoting organizational learning. In conjunction with correction and deviation management, these processes are integral to maintaining a robust and effective QMS.

(Textr from Section 3: Quality Management Systems (QMS) from an MDR Perspective - Subsection 6: Measurement, Analysis, and Improvement)

The QMS must include processes for (1) monitoring and measuring product performance, (2) analysing data and (3) implementing improvements.

1) **Monitoring and Measurement:**
   Input for CA and PA may originate from many resources:
   - Performance Metrics: Develop key performance indicators (KPIs) tailored to drug-device combination products. Metrics should include device reliability, drug delivery accuracy, failure rates, and customer complaints.
   - Data Collection: Implement comprehensive data collection systems throughout the product lifecycle. This includes manufacturing data (including nonconforming process), quality control results (including nonconforming product / service), clinical performance data and post-market surveillance (including serious adverse events, adverse device effects and device deficiencies).
   - In-Process Monitoring: Continuously monitor critical manufacturing processes to correct or address if they do not operate within specified limits. Use tools such as Statistical Process Control (SPC) to detect variations and maintain quality consistency.
2) **Analysis:**
   - Data Analysis: Apply statistical methods to analyze performance data and identify negative trends, anomalies, or areas for improvement. Techniques like root cause analysis help determine underlying issues affecting product performance and contribute to the devices' risk management process.
   - Risk Management: Regularly conduct risk assessments to evaluate potential hazards and their impact on the device component. Update risk management plans based on new data and insights.
   - Performance Reviews: Hold regular performance reviews to assess the QMS's effectiveness. Evaluate the collected data against predefined objectives and regulatory requirements and to timely address potential corrective or preventive actions.
3) **Improvement:**

- Corrections: Actions to eliminate detected nonconformities.
- Corrective Actions: Develop and implement corrective actions to address identified issues or non-conformities. Ensure that these actions effectively resolve the problems and prevent recurrence.
- Preventive Actions: Identify potential issues before they occur and implement preventive measures. This proactive approach helps maintain product quality and compliance.
- Improvement: Foster a culture of improvement to ensure and maintain the continued suitability - and even the continuous improvement, adequacy, and effectiveness of the QMS using methodologies like Lean, Six Sigma, and Kaizen. Encourage all levels of the organization to participate in identifying and implementing improvements.
- Management Review: Conduct regular management reviews to evaluate the QMS's performance and improvement efforts. Use these reviews to set new quality objectives and ensure alignment with regulatory changes and business goals.

By integrating these processes into the QMS, manufacturers can ensure their drug-device combination products consistently meet regulatory requirements and deliver safe, effective performance. This comprehensive approach helps maintain compliance, enhance product quality, and improve patient outcomes.

## C. Background on Statistical Techniques

Applying statistical techniques is essential for ensuring product quality, validating processes, managing risks, designing sampling and testing protocols, complying with regulations, making data-driven decisions, and fostering continuous improvement. These practices collectively help meet regulatory requirements and ensure the safety and efficacy of medical devices and drugs.

(Taken from Section 3: Quality Management Systems (QMS) from an MDR Perspective - Subsection 3: Quality Management System (Apply risk-based approach to the control of the appropriate needed processes), Subsection 6: Measurement, Analysis, and Improvement - Section 4: Post-Market Surveillance)

**Various sections of ISO 13485:2016 address the application of statistical techniques:**

- **§7.3.6 Design and Development (D&D) verification**:
  The organization shall document verification plans that include methods, acceptance criteria and, as appropriate, statistical techniques with rationale for sample size.
- §**7.3.7 D&D validation**:

The organization shall document validation plans that include methods, acceptance criteria and, as appropriate, statistical techniques with rationale for sample size.

- **§7.5.6 Validation of processes for production and service provision**:
  The organization shall validate any processes for production and service provision where the resulting output cannot be or is not verified by subsequent monitoring or measurement and, as a consequence, deficiencies become apparent only after the product is in use or the service has been delivered. Validation shall demonstrate the ability of these processes to achieve planned results consistently.
  The organization shall document procedures for validation of processes, including, as appropriate, statistical techniques with rationale for sample sizes.
- **§8 (Measurement, analysis and improvement) §8.1 General**:
  The organization shall plan and implement the monitoring, measurement, analysis and improvement processes needed to:
  (a) demonstrate conformity of product;
  (b) ensure conformity of the quality management system;
  (c) maintain the effectiveness of the quality management system.
  This shall include determination of appropriate methods, including statistical techniques, and the extent of their use.
- **§8 (Measurement, analysis and improvement) §8.4 Analysis of data**:
  The organization shall document procedures to determine, collect and analyze appropriate data to demonstrate the suitability, adequacy and effectiveness of the quality management system. The procedures shall include determination of appropriate methods, including statistical techniques and the extent of their use.