Pharmaceutical Quality by Design

Quality-by-design (QbD) is a systematic approach to designing and developing a product/service based on sound science and quality risk management. It is frequently applied in the pharmaceutical industry, mainly in developing pharmaceutical products and analytical methods. Still, it needs to be better established in setting up facilities like a quality control laboratory (QC lab). [1]

Elements of Quality by Design: [2]

1. **Quality Target Product Profile (QTPP):** defines the desired characteristics of the drug product and identifies its critical quality attributes (CQAs).
2. **Product Design and Understanding:** involves identifying the critical material attributes (CMAs) that affect the product's quality.
3. **Process Design and Understanding:** identifying critical process parameters (CPPs) and linking them with CMAs and CQAs to ensure product quality.
4. **Control Strategy**: includes setting specifications for the drug substance, excipients, and the final product, along with controls for each manufacturing step.
5. **Process Capability and Continuous Improvement:** evaluating the process performance and making ongoing enhancements to maintain quality.

PHARMACEUTICAL QUALITY BY DESIGN OBJECTIVES

Pharmaceutical Quality by Design is an advanced and systematic approach to development that prioritizes predefined objectives. It emphasizes comprehensive understanding and control of the product and the process based on rigorous science and quality risk management. The key objectives of pharmaceutical QbD include: [1]

1. Establish meaningful product quality specifications rooted in clinical performance.

2. Enhance process capability while reducing product variability and defects by optimizing product and process design, understanding, and control.

3. Improve product development and manufacturing efficiencies.

4. Strengthening root cause analysis and post-approval change management.

Under Quality-by-Design, achieving quality goals often involves connecting product quality to the desired clinical performance and designing a robust formulation and manufacturing process to meet this quality consistently. Since introducing pharmaceutical QbD, the FDA has made notable progress toward establishing performance-based quality specifications. For instance, FDA policies now address tablet

scoring and the size of beads in capsules labeled for sprinkles. Recent FDA discussions have also focused on assayed potency limits for narrow therapeutic index drugs and the physical attributes of generic drug products. However, while ICH guidelines did not explicitly recognize clinical performance-based specifications as a QbD objective, this has been acknowledged in recent scientific literature. [3-4]

The second goal of pharmaceutical QbD is to enhance process capability and minimize product variability, which often leads to defects, rejections, and recalls. Achieving this requires robust product and process design, alongside a deeper understanding of the factors influencing drug product quality. Post-regulatory approval, ongoing efforts should focus on process improvement to further reduce variability and defects. [5-7]

Table 1- Beckman Coulter Life Sciences Products with Unique Feature

Instrument	Support Regulations	**Features**
MET ONE 3400+ Air Particle Counter	EU GMP Annex 1 CGMP ISO 14644-1 & -2	• The LDAP (Lightweight Directory Access Protocol) is designed for an Active Directory. • Onscreen instructions help operators navigate your map and perform sampling according to the SOP. • Managers can review daily monitoring progress, including all sample results and alarms, via a web browser. • An electronic signature is attached to all approved final reports, which can then be exported in a secure electronic format.
Anatel PAT700 Online TOC Analyzer	USP<643> USP<645> EP2.2.44 EP2.2.38	• User can pre-program the PAT700 analyzer so that at a pre-determined TOC level, it will capture a water sample, which can then be later analyzed in the QC Lab to assist root cause analysis should a TOC excursion be detected • On-board grab sampler allows the user to take samples from different locations/use points to support root cause analysis
QbD1200+ Lab TOC Analyzer	USP<643> EP2.2.44	• Reduces sample-to-sample carryover • Streamlined, secure data management • Simplified reporting, encrypted data, secure protocol • Auto-range and auto-dilution of concentrated samples
LS 13 320 XR Particle Size Analyzer	USP<429>(excluding DPS)	• Laser diffraction plus advanced Polarization Intensity Differential Scattering (PIDS) technology enable high-resolution measurement & reporting of accurate data down to 10 nm • Provides accurate, reliable detection of multiple particle sizes in a single sample
Multisizer 4e Coulter Counter	USP<787>, <788>, <1787> and <1788>	• Accurate determination of sample cell number, size, and concentration • The Coulter method is the only “direct” method for studying particle volume • Analysis of a single cell per unit of time • Real-time detection of changes in the average cell size
MET ONE Facility Monitoring System	EU GMP Annex 1 CGMP ISO 14644-2	• Nonviable and viable particle monitoring compliant with EU GMP • Built-in Audit Logging • Custom reports to record results • IQ/OQ documentation for simple validation
HIAC 9703+ Pharmaceutical Particle Counter	USP<787>, <788>, <1787> and <1788>	• Instant particle contamination notification • Small vial holder & tare volume conserve costly samples • Program custom SOPs to eliminate manual counter configuration and pass/fail calculations • Automatic database backup & recovery loss feature protects valuable results and data

QbD's systematic approach to product design and development enhances development capabilities, speeds up formulation design, and shifts resources from a reactive, corrective stance to a proactive one. This approach improves the manufacturer's

ability to pinpoint the root causes of manufacturing failures, thus increasing product development and manufacturing efficiency.[6-7]

The main goal of Quality by Design is to enhance the process of identifying the underlying cause of issues and managing changes after a product has been approved. Scaling up production efficiently and conducting root cause analysis becomes difficult without a deep understanding of the scientific tools involved in the production and process. This may necessitate additional data for larger-scale operations. The FDA's guidance on post-approval changes provides a framework for managing such changes, with recent updates designed to reduce regulatory filing requirements for specific low-risk chemistry, manufacturing, and control (CMC) post-approval changes. Beckman Coulter Life Sciences' product lines are integral to ensuring accurate data and monitoring production for security and functionality (Table 1).

References:

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2- Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014 Jul;16(4):771-83

3- U.S. Food and Drug Administration. Guidance for Industry: Tablet Scoring: Terminology, Labeling, and Data for Evaluation. 2013.

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7- U. S. Food and Drug Administration. Guidance for industry: CMC post-approval manufacturing changes will be documented in annual reports. 2014.

8- ALCOA – A QC Suite Made 4 Pharma – App note DocID: 21.06.1781.PCC

9- Quality Control Electronic Records for 21CFR part 11 Compliance – App note DocID: P ART-1935WP08.16

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