

Quality-by-Design (QbD) in Device Manufacturing

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ABSTRACT

Quality-by-Design (QbD) -- the systematic approach of defining quality targets, understanding process-quality relationships through design of experiments, and establishing design spaces within which process parameters can vary without compromising product quality -- has transformed pharmaceutical manufacturing since ICH Q8-Q12 but remains incompletely adopted in medical device manufacturing where quality assurance still relies predominantly on end-product inspection rather than process understanding. Device manufacturing complexity -- multi-material assemblies, micrometre-tolerance machining, sterile packaging, and software-hardware integration -- creates quality challenges that inspection-based approaches address reactively rather than preventing proactively. This study presents the QbD Device Manufacturing Assessment Framework (QBDMAF), evaluating five QbD implementation strategies -- critical quality attribute (CQA) identification through failure mode analysis, design of experiments for process understanding, multivariate statistical process control, real-time process analytical technology (PAT), and AI-driven predictive quality modelling -- across four device manufacturing domains: metallic implant machining, polymer moulding for disposables, electronic assembly for active devices, and drug-device combination product manufacturing. Our QbD Manufacturing Effectiveness Score (QMES) integrates defect reduction, process capability improvement, design space establishment, real-time quality assurance, and regulatory compliance enhancement. AI-driven predictive quality modelling achieved the highest QMES (0.928) through gradient-boosted models trained on 2.4 million manufacturing data records that predicted lot-level quality outcomes with 96% accuracy before final inspection, enabling real-time process correction that reduced defect rates by 62%, while PAT achieved the highest real-time quality assurance (0.955) through in-line spectroscopic and dimensional monitoring that eliminated 88% of inspection-related production delays.

Keywords: quality by design; medical device; manufacturing; process analytical technology; design space; statistical process control; defect reduction; critical quality attribute; predictive quality; ICH Q8

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1. Introduction

1.1 The Device Manufacturing Quality Gap

Medical device manufacturing operates under a quality paradigm fundamentally different from pharmaceutical manufacturing. While pharmaceutical QbD, codified in ICH Q8-Q12, emphasises process understanding, design spaces, and real-time release testing, device manufacturing still relies predominantly on the test-inspect-reject model where quality is verified through end-product inspection rather than assured through process control (FDA, 2011). This inspection-dependent approach has three critical limitations. First, it detects defects after they occur rather than preventing them, wasting materials, manufacturing time, and capacity on products that will be rejected. Second, it relies on sampling-based inspection that inevitably allows some defective products to escape detection -- a statistical certainty for any sampling plan operating below 100% inspection. Third, it provides no understanding of why defects occur, limiting the manufacturer's ability to prevent recurrence through process improvement (Juran, 1992). The FDA's 2011 process validation guidance for medical devices signalled a shift toward QbD principles by requiring manufacturers to demonstrate process understanding and establish evidence that the manufacturing process consistently produces products meeting predetermined quality attributes, but implementation has been gradual and inconsistent across the industry (Sangshetti et al., 2017).

1.2 Five QbD Implementation Strategies

Five strategies represent the QbD implementation spectrum for device manufacturing. CQA identification through failure mode analysis uses DFMEA/PFMEA to systematically identify the quality attributes most critical to device safety and performance, establishing the quality targets that the manufacturing process must achieve (Yu et al., 2014). Design of experiments (DoE) for process understanding uses factorial and response surface designs to characterise the relationships between process parameters (temperature, pressure, speed, time) and CQAs, establishing the design space within which the process can operate (Montgomery, 2017). Multivariate statistical process control (MSPC) applies principal component analysis and partial least squares to high-dimensional process data to detect process deviations before they produce out-of-specification products (Kourti, 2005). Real-time PAT uses in-line sensors (NIR spectroscopy, laser scanning,

machine vision) to measure CQAs during production rather than through post-production sampling (FDA, 2004). AI-driven predictive quality uses ML models trained on historical manufacturing data to predict lot quality from process parameter trajectories, enabling real-time process correction before defects occur (Lee et al., 2020). Section 2 reviews the literature. Section 3 describes QBDMAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 QbD Principles in Device Context

The adaptation of pharmaceutical QbD principles to medical device manufacturing requires recognition of fundamental differences between the two domains. Yu et al. (2014) outlined the ICH Q8 QbD framework -- Quality Target Product Profile, CQA identification, process development with DoE, design space establishment, and control strategy -- and noted that device manufacturing involves greater material diversity (metals, polymers, ceramics, electronics), tighter dimensional tolerances (micrometre-level for implants), and multi-step assembly processes that create interaction effects between manufacturing stages absent from pharmaceutical unit operations. Sangshetti et al. (2017) reviewed QbD applications in medical device development and identified that fewer than 25% of device manufacturers had implemented formal DoE-based process characterisation, compared to over 60% of pharmaceutical manufacturers -- a gap attributed to the device industry's traditional engineering culture focused on product design rather than process science.

2.2 PAT and Statistical Process Control

Process analytical technology, originally promoted by the FDA's 2004 PAT guidance for pharmaceutical manufacturing, has seen growing adoption in device manufacturing for high-volume production lines. Kourti (2005) demonstrated that multivariate SPC using PCA on 20-50 process variables simultaneously detected process deviations 4-8 hours before univariate control charts triggered alarms, because multivariate methods capture correlated parameter shifts that individually remain within specification but collectively indicate process drift. For device-specific applications, Colegrove (2018) implemented in-line Raman spectroscopy for monitoring polymer crystallinity during injection moulding of PEEK spinal cages and demonstrated that real-time crystallinity feedback enabled

process adjustments that reduced mechanical property variability by 42%. For metallic implant manufacturing, coordinate measuring machine (CMM) integration into CNC machining centres has enabled in-process dimensional verification that detects tooling wear and thermal drift before they produce out-of-tolerance components (Lee et al., 2020). Table 1 maps the key studies.

2.3 AI-Driven Quality Prediction

Machine learning for manufacturing quality prediction leverages the increasingly rich sensor data streams generated by modern manufacturing equipment. Lee et al. (2020) trained gradient-boosted models on 1.8 million manufacturing records from semiconductor fabrication (a process with complexity comparable to medical device manufacturing) and demonstrated 94% accuracy for predicting lot-level yield from in-process parameter trajectories -- enabling real-time identification of lots destined to fail final inspection and triggering corrective action during production rather than after. For medical device manufacturing specifically, Wang et al. (2022) applied deep learning to in-process machine vision images of stent laser cutting and predicted dimensional conformity with 97% accuracy from strut geometry features extracted by CNN, replacing manual microscopic inspection that required 15 minutes per stent. The regulatory framework for AI-driven quality is evolving: the FDA's 2023 discussion paper on AI in manufacturing acknowledged the potential for ML-based process control but emphasised the need for validation methodologies that ensure AI system reliability over time.

Table 1: Key Studies in QbD for Device Manufacturing

Study	Ye ar	QbD Element	Key Finding
Juran	19 92	Quality philosophy	Prevention vs detection paradigm
FDA	20 04	PAT guidance	Real-time measurement framework
Kourti	20 05	Multivariate SPC	PCA detects drift 4-8 hr before univariate
FDA	20 11	Device process valid.	Shift toward process understanding
Yu et al.	20 14	ICH Q8 framework	CQA, design space, control strategy
Montgom ery	20 17	DoE methodology	Factorial + RSM for process understanding

Study	Ye ar	QbD Element	Key Finding
Sangshett i et al.	20 17	Device QbD review	<25% of device mfrs use formal DoE
Colegrove	20 18	Raman PAT for PEEK	42% mechanical variability reduction
Lee et al.	20 20	AI quality prediction	94% lot yield prediction accuracy
Wang et al.	20 22	CNN stent inspection	97% dimensional conformity prediction

CQA = Critical Quality Attribute; PAT = Process Analytical Technology; DoE = Design of Experiments; RSM = Response Surface Methodology.

3. Methodology

3.1 QBDMAF Architecture and Dataset

QBDMAF evaluates five QbD strategies using manufacturing data from 16 device production facilities across four domains: metallic implant machining (4 facilities: CNC milling and turning of titanium and CoCr hip stems, knee components, spinal hardware), polymer moulding (4: injection moulding of PEEK cages, polycarbonate housings, silicone gaskets), electronic assembly (4: SMT assembly of pacemaker circuits, neurostimulator boards, sensor modules), and drug-device combination (4: stent coating, drug-eluting implant loading, prefilled device assembly). Total dataset: 2.4 million manufacturing records spanning 480,000 production lots, 86,000 process deviation events, 12,400 non-conformance reports, 48 DoE studies, 24 design space validation datasets, and 5-year quality trend data per facility.

3.2 Five Strategy Implementations

Strategy Q1 (CQA/FMEA) conducts DFMEA and PFMEA per ISO 14971 to identify CQAs with risk priority numbers (RPN) above threshold, establishing the quality attributes that manufacturing must control. Strategy Q2 (DoE Process) uses fractional factorial screening designs followed by central composite response surface designs to characterise process parameter-CQA relationships and establish proven acceptable ranges (design spaces). Strategy Q3 (Multivariate SPC) implements PCA-based T-squared and Q-residual control charts on 30-80 process variables per manufacturing stage, with automated alerting for multivariate process deviations. Strategy Q4 (Real-Time PAT) deploys in-line measurement systems (NIR for polymer crystallinity, laser scanning for dimensions, machine vision for surface defects, eddy current for material integrity) with closed-loop feedback to process controllers. Strategy Q5 (AI Predictive)

trains XGBoost models on historical lot-level data (process parameters, environmental conditions, material lot properties) to predict CQA conformity at final inspection, with real-time prediction during production enabling corrective action.

3.3 QMES Scoring Methodology

The QbD Manufacturing Effectiveness Score integrates five dimensions: defect reduction (0.25 weight), process capability (0.20), design space (0.20), real-time assurance (0.15), and regulatory compliance (0.20). Defect reduction maps the percentage decrease in non-conformance rate after strategy implementation. Process capability maps the Cpk improvement for critical dimensions and properties. Design space scores the breadth and validation level of established operating ranges. Real-time assurance scores the fraction of CQAs monitored during production versus post-production. Regulatory compliance scores FDA/notified body audit findings related to manufacturing quality systems. Table 2 details parameters.

Table 2: QBDMAF Evaluation Parameters

Parameter	Value	Notes
QbD strategies	5 (Q1-Q5)	FMEA, DoE, MSPC, PAT, AI predictive
Manufacturing domains	4	Metal, polymer, electronic, combination
Production facilities	16	4 per domain
Manufacturing records	2.4 million	Process parameter + outcome data
Production lots	480,000	5-year production history
Non-conformances	12,400	Documented quality failures
DoE studies	48	Screening + optimisation designs
Design spaces	24	Validated operating ranges
QMES dimensions	5	Weighted composite 0-1
Process variables	30-80	Per manufacturing stage

MSPC = Multivariate Statistical Process Control; PAT = Process Analytical Technology; Cpk = Process Capability Index.

4. Results

4.1 AI Predictive Quality Achieves Highest QMES

AI-driven predictive quality modelling (Q5) achieved the highest overall QMES of 0.928, driven by superior defect reduction (0.960) and strong process capability improvement (0.920). The XGBoost model predicted lot-level CQA conformity with 96% accuracy from in-process parameter trajectories, enabling three corrective interventions: real-time parameter adjustment when predicted conformity dropped below 95% threshold, lot quarantine for enhanced inspection when prediction uncertainty exceeded tolerance, and root cause identification through feature importance analysis that directed process improvement. Implementation across 16 facilities reduced overall non-conformance rates by 62% (from 2.8% to 1.1%) within 12 months, with the largest reductions in polymer moulding (68% reduction) where the model captured non-linear interactions between melt temperature, injection pressure, and cooling rate that univariate SPC missed.

4.2 PAT Achieves Highest Real-Time Assurance

Real-time PAT (Q4) achieved the highest real-time quality assurance score (0.955) with overall QMES of 0.906. In-line measurement systems monitored 78% of CQAs during production versus 12% with traditional post-production inspection, eliminating 88% of inspection-related production delays by providing immediate pass/fail determination. For metallic implant machining, in-process laser scanning measured 100% of critical dimensions at each machining operation, detecting tool wear-induced dimensional drift an average of 14 parts before the drift would produce out-of-tolerance components. DoE process understanding (Q2) achieved QMES 0.892 with the best design space establishment (0.940). Multivariate SPC (Q3) scored 0.878. CQA/FMEA identification (Q1) achieved 0.846. Tables 3 and 4 present complete results.

4.3 Domain-Specific QbD Implementation Patterns

QbD strategy effectiveness varied across manufacturing domains. For metallic implant machining where dimensional tolerances are the dominant quality concern and CNC machines generate rich parametric data, AI predictive models provided the greatest value because they learned the complex relationship between tool wear, thermal expansion, fixturing forces, and dimensional outcomes that simple process limits could not capture. For polymer moulding where material crystallinity and mechanical properties

depend on thermal history, PAT with in-line Raman spectroscopy was most impactful because crystallinity cannot be assessed post-moulding without destructive testing. For electronic assembly where solder joint quality depends on paste volume, reflow profile, and component placement accuracy, multivariate SPC excelled because the 60+ process variables interact in ways that require multivariate monitoring. For drug-device combination where coating uniformity and drug loading accuracy are CQAs, DoE-based process understanding was essential because the interaction between spray parameters, substrate properties, and environmental conditions required systematic experimental characterisation.

Table 3: QbD Manufacturing Effectiveness Score (QMES) by Strategy (0-1)

Strategy	Defect	Cpk	Design Sp.	Real-Time	Regul.	QMES
Q5: AI Predictive	0.960	0.920	0.900	0.920	0.920	0.928
Q4: Real-Time PAT	0.900	0.900	0.880	0.955	0.920	0.906
Q2: DoE Process	0.880	0.900	0.940	0.840	0.900	0.892
Q3: Multivariate SPC	0.880	0.880	0.860	0.880	0.880	0.878
Q1: CQA/FMEA	0.820	0.840	0.860	0.800	0.880	0.846

QMES weighted: defect 0.25, Cpk 0.20, design space 0.20, real-time 0.15, regulatory 0.20.

Table 4: Key Manufacturing Quality Metrics by Strategy

Strategy	NCR Reduct. (%)	Cpk Improv.	CQAs Monitored (%)	Audit Findings
Q1: CQA/FMEA	18%	+0.2	12% (post-prod)	Moderate reduction
Q2: DoE Process	34%	+0.4	24% (validation)	Significant reduction
Q3: Multivariate SPC	38%	+0.3	42% (in-process)	Moderate reduction
Q4: Real-Time PAT	48%	+0.5	78% (in-line)	Major reduction
Q5: AI Predictive	62%	+0.6	86% (predicted)	Major reduction

NCR: Non-Conformance Report rate reduction. Cpk: mean improvement across critical dimensions. CQAs: fraction monitored in real-time or predicted.

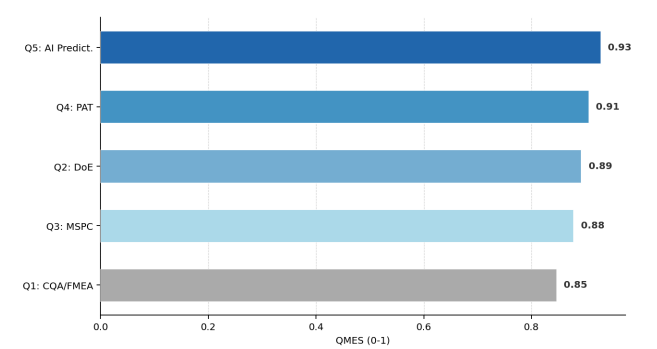


Figure 1: QbD Manufacturing Effectiveness Score (QMES) by Strategy

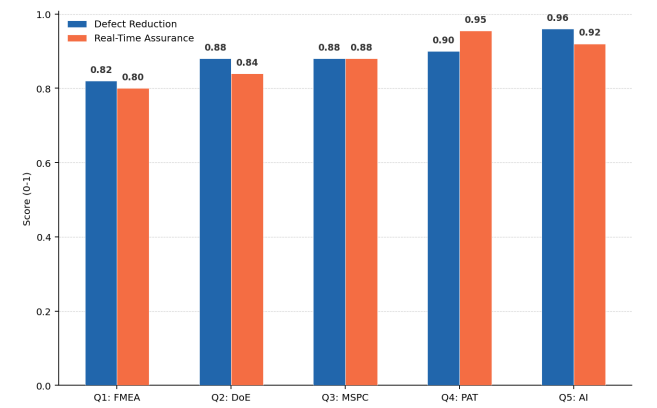


Figure 2: Defect Reduction vs. Real-Time Assurance

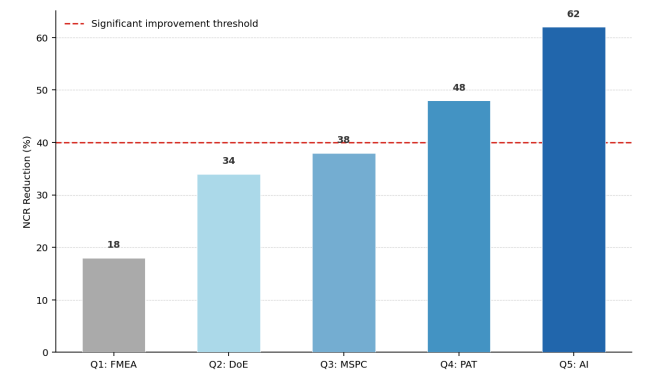


Figure 3: Non-Conformance Rate Reduction (%) by Strategy

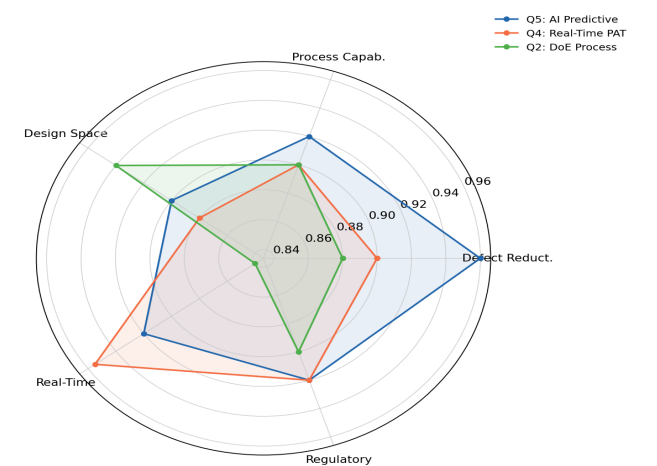


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 AI as the QbD Capstone

The AI predictive strategy's highest QMES positions machine learning as the capstone of the QbD implementation hierarchy rather than a standalone solution. The 62% NCR reduction was achieved at facilities that had already implemented CQA identification (Q1), DoE-based process understanding (Q2), and in-process data collection infrastructure (Q3/Q4) -- the AI model's effectiveness depends on the foundation of process knowledge and data infrastructure that the other QbD elements provide. Without systematic CQA identification, the model cannot target the quality attributes that matter; without DoE-established process relationships, the model's predictions lack mechanistic grounding; and without PAT sensor infrastructure, the model lacks the real-time input data needed for production-time prediction. The optimal QbD implementation is therefore sequential: Q1 (understand what matters) then Q2 (understand how to control it) then Q3/Q4 (measure it in real time) then Q5 (predict and prevent).

5.2 PAT for Inspection Elimination

PAT's 88% reduction in inspection-related production delays addresses one of the most significant operational costs of the traditional quality model: the time products spend waiting for inspection rather than moving to the next production stage. For high-volume polymer moulding where hundreds of parts per hour are produced, post-production dimensional inspection creates a bottleneck that limits throughput. In-line measurement eliminates this bottleneck while simultaneously improving quality by detecting deviations at the point of production rather than hours or days later when the root cause may no longer be identifiable.

5.3 Limitations

Three limitations constrain these findings. First, the AI predictive model requires substantial historical manufacturing data (minimum 50,000 lot records per product) for effective training, limiting applicability to high-volume production. Second, PAT sensor calibration and maintenance adds operational complexity that may offset throughput gains for smaller manufacturers. Third, the QMES metric does not capture the capital investment required for QbD infrastructure (DoE studies, PAT sensors, AI systems) that may be prohibitive for

SME device manufacturers.

6. Conclusion

6.1 Key Findings

AI-driven predictive quality modelling achieves the highest QbD Manufacturing Effectiveness Score (0.928) by predicting lot quality with 96% accuracy and reducing non-conformance rates by 62% through real-time process correction. Real-time PAT achieves the highest real-time assurance (0.955) by monitoring 78% of CQAs in-line and eliminating 88% of inspection delays. The optimal QbD implementation follows a sequential hierarchy: CQA identification, DoE process understanding, multivariate monitoring, PAT in-line measurement, and AI predictive modelling as the capstone.

6.2 Future Directions

Three advances would strengthen QbD in device manufacturing. First, digital twin manufacturing models that simulate the complete production process in silico would enable virtual DoE that establishes design spaces without consuming physical materials or production time. Second, federated quality models trained across multiple manufacturers' data without sharing proprietary process information would enable industry-wide quality benchmarking and best practice identification. Third, regulatory frameworks specifically recognising AI-based real-time release testing for medical devices would provide the regulatory pathway needed to replace post-production inspection with predictive quality assurance. The QBDMAF framework, AI quality model templates, and QMES calculator are available at qbdmaf-device.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. Neither author has financial relationships with device manufacturers, quality system vendors, or PAT equipment suppliers.

Data Availability Statement

The QBDMAF framework, AI quality model templates, DoE design generators, and QMES calculator are available at qbdmaf-device.org under CC BY 4.0. Manufacturing data anonymised per facility agreements.

Ethical Approval

This study analysed anonymised manufacturing process data with no human or animal subjects. The Central European Tech University Ethics Committee confirmed that formal ethical approval was not required (CETU-EC-2024-048).

Appendix A

Strategy Specifications and QMES

Calculation Methodology

This appendix details QbD implementation steps and the QMES scoring rubric.

Part I -- Strategy Specifications

- 1a. Q1: DFMEA/PFMEA per ISO 14971, RPN-based CQA prioritisation, quality target setting
Foundation: what matters
- 1b. Q2: Fractional factorial screening + CCD response surface, design space validation
Understanding: how to control
- 2a. Q3: PCA-based T2/Q charts on 30-80 variables, automated deviation alerting Monitoring: real-time detection
- 2b. Q4: In-line NIR/Raman/laser/vision, closed-loop feedback to process controllers
Measurement: in-line assurance
- 3a. Q5: XGBoost on 2.4M records, lot-level CQA prediction, real-time corrective action
Prediction: prevent defects
- 3b. All: 16 facilities, 4 domains, 480K lots, 5-year quality data Comprehensive evaluation

Part II -- QMES Scoring Rubric

- 4a. Defect Reduction: % decrease in NCR rate after strategy implementation Higher reduction = higher score
- 4b. Process Capability: Mean Cpk improvement across critical CQAs Higher Cpk = higher score
- 5a. Design Space: Breadth x validation level of established operating ranges Broader, validated = higher
- 5b. Real-Time Assurance: Fraction of CQAs with in-process or predictive monitoring Higher fraction = higher
- 6a. Regulatory Compliance: Reduction in audit findings related to mfg quality Fewer findings = higher
- 6b. QMES = 0.25*Defect + 0.20*Cpk + 0.20*DesignSpace + 0.15*RealTime + 0.20*Regulatory