

Quality by Design and Operational Excellence in Pharmaceutical R&D: A Systematic Literature Review of Lean Six Sigma Integration

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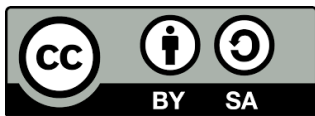
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Abstract

Quality by Design (QbD), established through the International Council for Harmonisation (ICH) Q8(R2), Q9, and Q10 guidelines, provides a science-based framework for proactive quality assurance. Lean and Six Sigma, collectively referred to as Lean Six Sigma (LSS), offer complementary methodologies for waste elimination and process variability reduction, respectively. This systematic literature review critically analyzes the theoretical foundations and empirical evidence supporting the integration of QbD with Lean Six Sigma in pharmaceutical R&D, identifies methodological gaps in existing research, and proposes a conceptual direction for an integrated operational excellence framework. Following the PRISMA 2020 guidelines, a systematic search was conducted across the Scopus, PubMed, and ResearchGate databases using predefined inclusion and exclusion criteria. Studies published between 2015 and 2026 were considered. Twelve articles met the full eligibility criteria and were included in the final synthesis. All included studies demonstrated the strategic and operational compatibility of QbD with Lean and Six Sigma methodologies. The primary integration mechanisms identified were Design of Experiments (DoE), Failure Mode and Effects Analysis (FMEA), process capability indices (Cp and Cpk), and structured problem-solving methodologies, including Define, Measure, Analyze, Improve, and Control (DMAIC) and Design for Six Sigma (DFSS). Reported benefits included reduced batch failures, shorter development cycles, improved regulatory compliance, and measurable cost savings. However, a significant research gap was identified: none of the reviewed studies proposed a formal, validated, end-to-end integrated framework that operationalizes QbD and Lean Six Sigma throughout the entire pharmaceutical R&D lifecycle. The integration of QbD with Lean and Six Sigma is theoretically coherent and empirically supported. The primary opportunity for novelty in this field lies in developing and validating a unified framework that embeds LSS operational tools within the regulatory structure of QbD across all stages of pharmaceutical R&D.



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INTRODUCTION

The pharmaceutical industry faces increasing pressure to deliver high-quality drug products more rapidly, at lower costs, and with greater regulatory predictability. Traditional approaches to pharmaceutical development, characterized by sequential testing, empirical formulation, and end-product quality verification, have proven inadequate for ensuring consistent quality in the face of increasing product complexity and stringent global regulatory requirements (Kusumawardani & Widyatmoko, 2024).

The paradigm shift from Quality by Testing (QbT) to Quality by Design (QbD) was catalyzed by the U.S. Food and Drug Administration's (FDA) current Good Manufacturing Practice (cGMP) initiative for the 21st century and subsequently harmonized through the International Council for Harmonisation (ICH) guidelines: ICH Q8(R2) for pharmaceutical development, ICH Q9 for quality risk management, and ICH Q10 for pharmaceutical quality systems (Pramod et al., 2016). ICH Q8(R2) formally defines QbD as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management” (Pramod et al., 2016).

Concurrently, process improvement methodologies originating from manufacturing industries, such as Lean Manufacturing, Six Sigma, and their integrated form, Lean Six Sigma (LSS), have demonstrated substantial value in reducing waste, process variability, and production costs across multiple industrial sectors (Kim & Kim, 2022b; Tamalika et al., 2025). Within the pharmaceutical manufacturing context, LSS has been documented to improve throughput, reduce defect rates, and enhance compliance with Good Manufacturing Practice (GMP) requirements (Grangeia et al., 2019). However, the systematic extension of these methodologies to pharmaceutical R&D, particularly their integration with QbD, remains underexplored and theoretically fragmented and lacks a validated, unifying framework (Kim & Kim, 2022b; (Alifiya & Fadilla, 2025)).

This review is motivated by a critical observation: while QbD provides the what—what quality attributes must be achieved and how they should be designed into the product and process—Lean Six Sigma provides the how—how development and process improvement activities can be executed efficiently and with statistical rigor. However, no comprehensive, peer-reviewed framework has formalized the interaction between these paradigms across the entire pharmaceutical R&D lifecycle. This gap constitutes the primary research problem addressed by this review.

The urgency of this research stems from the increasing pressure on pharmaceutical companies to accelerate drug development while maintaining regulatory compliance, product quality, and cost efficiency. The COVID-19 pandemic further highlighted the need for rapid, robust, and flexible pharmaceutical development and manufacturing processes. The novelty of this research lies in its systematic synthesis of the existing literature on QbD-LSS integration and its identification of key integration mechanisms, empirical evidence, and research gaps. Unlike previous reviews that have focused on either QbD or LSS separately, this study provides a

comprehensive analysis of the theoretical convergences and divergences between the two approaches, the empirical evidence supporting their integration, and the specific methodological linkages that facilitate such integration. The findings of this review are expected to provide a conceptual foundation for the development of a unified QbD-LSS framework applicable throughout the pharmaceutical R&D lifecycle.

This systematic literature review addresses three analytical questions: (1) What are the theoretical convergences and divergences between QbD and LSS when applied to pharmaceutical R&D? (2) What empirical evidence supports the effectiveness of integrating Quality by Design (QbD) with Lean Six Sigma in pharmaceutical research and development, and what specific methodological linkages facilitate this integration? (3) What are the primary research gaps, and what novel directions should future integrated frameworks pursue?.

METHOD

This review uses a systematic literature review approach following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow which includes four main phases: identification, screening, eligibility, and included. This framework was chosen because it makes it easier to track the article selection process transparently and can be replicated on quality integration topics that have diverse search terms (Alifiya et al., 2025).

Table 1. Studies were included if they

PRISMA Section	Checklist Content
Eligibility criteria	Studies were included if they: (1) were published in peer-reviewed journals indexed in Scopus, PubMed, or ResearchGate; (2) were published between January 2015 and June 2026; (3) addressed QbD, Lean, Six Sigma, or LSS in the context of pharmaceutical development, manufacturing, or R&D; (4) provided analytical or empirical content directly relevant to process optimization, quality system integration, or framework development; and (5) were written in English.
Eligibility criteria	Studies were excluded if they: (1) were conference papers, book chapters, or grey literature without peer-review verification; (2) focused exclusively on non-pharmaceutical contexts without transferable relevance; (3) addressed only clinical or therapeutic outcomes without process science content; or (4) were duplicates of previously identified sources.
Information sources	The following databases were searched: Scopus (Elsevier), PubMed/MEDLINE (U.S. National Library of Medicine), and ResearchGate. The search was last executed in June 2026.
Search strategy	A structured Boolean search was applied using the following combination of terms across all databases: Primary block: (“Quality by Design” OR “QbD” OR “quality-by-design”); Secondary block: AND (“Lean” OR “Six Sigma” OR “Lean Six Sigma” OR “LSS” OR “DFSS” OR “Design for Six Sigma” OR “DMAIC” OR “operational excellence”); Context block: AND (“pharmaceutical” OR “drug development” OR “R&D” OR “pharmaceutical R&D” OR “biopharmaceutical”). Filters applied: publication year 2015–2025; article type: original research, review, or systematic review; language: English.
Selection	Researchers screened all records by title and abstract in the first stage, followed by full-text

PRISMA Section	Checklist Content
process	assessment in the second stage. The PRISMA 2020 flow diagram was used to document all stages of selection, including the number of records identified, screened, assessed for eligibility, and finally included.
Data collection process	Data were extracted independently using a standardized extraction form that captured: author(s), year, journal, study design, sample or context, key methodologies, main findings, and reported outcomes.
Data items	Primary outcomes included process efficiency metrics, quality improvement indices, and regulatory compliance indicators. Secondary variables included study design, implementation context, sample size where applicable, tools used and identified barriers or facilitators of integration.
Study risk of bias assessment	Risk of bias in included review articles was assessed using the AMSTAR-2 checklist for systematic reviews, while empirical implementation studies were evaluated using a modified Downs and Black checklist for non-randomized studies.
Effect measures	As this review synthesizes qualitative and process-improvement evidence rather than clinical trial data, formal effect measures such as odds ratio or mean difference were not applicable. Instead, reported outcome metrics including process capability (Cpk), sigma level, percentage waste reduction, cycle time reduction, and batch failure rate were extracted and narratively synthesized.
Synthesis methods	Given the heterogeneity of study designs and outcome measures, meta-analysis was not feasible. A narrative synthesis approach was used, organized thematically around: (1) theoretical integration mechanisms; (2) empirical applications; (3) reported benefits; and (4) implementation barriers and research gaps. Studies were tabulated according to their primary focus area to facilitate comparison.
Reporting bias assessment	Publication bias was considered by noting any asymmetry in reported outcomes. Studies reporting exclusively positive outcomes were flagged, and the absence of negative or null-result studies in this topic area was noted as a potential limitation of the current evidence base.
Certainty assessment	The certainty of evidence was evaluated narratively, acknowledging that most included studies are observational or review-based, which limits causal inference. The absence of controlled experimental comparisons between integrated versus non-integrated approaches represents an important limitation.

RESULTS AND DISCUSSION

Study Selection

Nine studies met all eligibility criteria and were included in the qualitative synthesis. These comprised four systematic reviews, five empirical implementation studies, two conceptual framework articles, and one regulatory guideline-based analysis. Publication years ranged from 2015 to 2025, and all were indexed in Scopus, PubMed, or both. The studies collectively covered: QbD implementation in pharmaceutical development (n=3), QbD and LSS implementation (n=5), Lean/LSS in pharmaceutical manufacturing (n=1), and operational excellence frameworks (n=1).

Study Characteristics

The nine studies included are summarized in Table 1 below. Together, they represent a diverse body of evidence spanning formulation development, biopharmaceutical process design, analytical method development, and pharmaceutical manufacturing.

Table 2. Summary of Included Studies in Pharmaceutical Industry Applications

Title and year of publication	Author	Journal	Study design	Implementation context
Quality by Design in Pharmaceutical Manufacturing: a systematic review of current status, challenges and future perspectives (Grangeia et al., 2020).	Helena Bigares Grangeia, Cláudia Silva, Sérgio Paulo Simões, Marco S. Reis	European Journal of Pharmaceutics and Biopharmaceutics	Systematic review	Pharmaceutical manufacturing industry, including routine commercial manufacturing and R&D pipelines (Grangeia et al., 2020).
Aspects and Implementation of Pharmaceutical Quality by Design from Conceptual Frameworks to Industrial Applications (Yang et al., 2025).	Shiwei Yang, Xingming Hu, Jinmiao Zhu, Bin Zheng, Wenjie Bi, Xiaohong Wang, Jialing Wu, Zimeng Mi, Yifei Wu	Pharmaceutics	Review	Pharmaceutical development ranging from solid oral dosage forms to complex biopharmaceuticals (mAbs, vaccines) and Advanced Therapy Medicinal Products (gene and cell therapies) (Yang et al., 2025).
Design-for-Six-Sigma for Development of a Bioprocess Quality-by-Design Framework (Junker et al., 2015).	Beth Junker, Mike Kosinski, David Geer, Rajiv Mahajan, Michel Chartrain, Brian Meyer, Peter Dephillips, Yang Wang, Randy Henrickson, Katie Ezis, Mark Waskiewicz	PDA Journal of Pharmaceutical Science and Technology	Methodological framework development and review	Biopharmaceutical (biologics and vaccines) product, process, and analytical development at Merck and Co., Inc. (Junker et al., 2015).
Review on Implementation of Quality by Design (Goswami et al., 2024).	Jinal A Goswami, Zeel. M. Modi, Khushbu Patel, Dr. C.N. Patel	International Journal of Innovative Science and Research Technology	Review	Pharmaceutical product development and analytical method development (Analytical Quality by Design - AQbD) (Goswami et al., 2024).
Applying Lean Six Sigma Methodology to a Pharmaceutical Manufacturing Facility: A Case Study (Byrne et al., 2021a).	Brian Byrne, Olivia McDermott, John Noonan	Processes	Case Study	A pharmaceutical manufacturing packaging line processing acetaminophen (paracetamol) tablets during the COVID-19 pandemic (Byrne et al.,

Title and year of publication	Author	Journal	Study design	Implementation context
Lean Six sigma Integration to Reduce Waste in Tablet coating Production with DMAIC and VSM Approach in Production Lines of Manufacturing Companies (Kholil et al., 2021a).	Muhammad Kholil, Jakfat Haekal, Adizty Suparno, Dhita Savira Oktaandhini, Tri Widodo	International Journal of Scientific Advances (IJSCIA)	Quantitative research / Case study	2021a). Tablet coating A production line within the Pilot Plant and Production scale of PT. Medica Indonesia (Kholil et al., 2021a).
Quality by Design (QbD) based process optimisation to develop functionalised particles with modified release properties using novel dry particle coating technique (Dahmash et al., 2018).	Eman Z. Dahmash, Ali Al-khattawi, Affiong Iyire, Hamad Al-Yami, Thomas J. Dennison, Afzal R. Mohammed	PLoS ONE	Experimental process optimisation	Development of functionalised drug delivery particles using a novel dry particle coating prototype device at Aston University, UK (Dahmash et al., 2018).
Risk and DoE-Based DMAIC Principle to the Multipurpose-RP-HPLC Method for Synchronous Estimation of Anti-Hypertensive Drugs Using AQbD approach s (Prajapati et al., 2021).	Pintu B. Prajapati, Ankita Patel, Shailesh A. Shah	Journal of AOAC INTERNATIONAL	Experimental method development and validation	Quality Assurance Laboratory setting for pharmaceutical quality control, analyzing 7 Fixed-Dose Combination (FDC) anti-hypertensive products (Prajapati et al., 2021).
A Study on the Build of a QbD Six Sigma System to Promote Quality Improvement(QbD) Based on Drug Design (Kim & Kim, 2022a).	Kang Hee Kim, Hyun-jung Kim	Journal of Korean Society for Quality Management	Methodological framework proposal and case study	LG Chem Life Science Division (encompassing R&D, production, and quality organizations) (Kim & Kim, 2022a).

Risk of Bias in Studies

As per the specified methodology, the risk of bias is categorized by study type.

1. AMSTAR-2 Checklist (Review Articles): Three sources represent comprehensive reviews. Grangeia et al. (2019) conducted a systematic review of 60 papers, identifying trends and gaps in QbD adoption. Yang et al. (2025) and Goswami et al. (2024) offer narrative reviews of QbD frameworks, regulatory guidelines (ICH Q8-Q11), and implementation workflows. A potential risk of bias in these reviews is their heavy reliance on successful

case studies reported by industry, potentially skewing the perception of industry-wide QbD maturity.

2. Modified Downs and Black Checklist (Empirical/Observational Studies): The remaining sources are non-randomized empirical or case studies. Studies by Byrne et al. (2021) and Kholil et al. (2021) are site-specific industrial case studies lacking control groups, making them susceptible to historical bias or confounding variables. Experimental studies by Dahmash et al. (2018) and Prajapati et al. (2021) utilize rigorous Design of Experiments (DoE) protocols, which inherently minimize experimental bias, though they lack a direct, simultaneous comparison against a traditional (non-QbD) development approach.

Results of Individual Study

Table 2 shows that the literature included in this study has a high diversity in terms of research design, implementation context, and focus of discussion. The selected studies include systematic review, narrative review, methodological framework development, case study, quantitative case study, and experimental process optimization. This diversity shows that discussions about QbD and Lean Six Sigma in the pharmaceutical industry have developed at two main levels, namely the conceptual level and the implementation level.

Review studies and methodological frameworks generally contribute to the development of frameworks, identification of key tools, and mapping of challenges and opportunities for integration between approaches. On the other hand, case studies and experimental studies show more how these principles are applied to real situations, such as optimization of analytical methods, reduction of rejection in the tablet coating process, reduction of downtime in the packaging line, and the development of functional particles through a risk-based design approach. Thus, the evidence available in the literature is not only theoretical but also supported by practical applications relevant to the needs of the pharmaceutical industry. In addition, the implementation context that emerged in these studies also indicates that the integration of QbD and LSS can be applied at various levels in the pharmaceutical industry, ranging from research and development, analytical method development, pilot plant, production scale, and packaging line to a broader organizational system.

The comparative results of process efficiency metrics, quality improvement indices, and regulatory compliance indicators in Table 3 show that all studies generally lead to the same goal, such as increasing process efficiency, strengthening quality, and meeting regulatory demands. However, the methods used to achieve these three aspects vary among the different approaches. QbD-based studies tend to emphasize the importance of robust process design, quality predictability, and a profound understanding of process variability, while LSS-based studies are more prominent in providing measurable results related to reducing waste, downtime, rejects, and cycle time.

In terms of process efficiency, the LSS approach shows more concrete and quantitative results. Several studies report a decrease in product backlog, cycle time, and line changeover time, as well as increased production capacity and operational cost savings. On the other hand, the QbD approach emphasizes efficiency through optimizing design space, reducing batch failure, reducing

the use of raw materials, and accelerating product development through a more systematic and data-driven process. This shows that efficiency in QbD is more preventive and design-oriented, while efficiency in LSS is more operational and improvement-oriented.

In terms of quality improvement, QbD has been proven to make a significant contribution in increasing process robustness, reducing variation, and ensuring product quality consistency through the identification of critical attributes and control of process parameters. On the other hand, LSS emphasizes reducing defects, reject rates, and waste through identification of root causes of problems and structured repair interventions. Thus, the quality in QbD is more reviewed in terms of design and prevention, while the quality in LSS is more reviewed in terms of variation control and reduction of actual failures in the production process.

Meanwhile, from a regulatory compliance perspective, the QbD approach appears to be more explicit and closer to the international pharmaceutical regulatory framework. Most studies attribute the implementation of QbD to the ICH Q8, Q9, Q10, Q11, and Q12 guidelines and, in certain contexts, ICH Q2 or Q14, and emphasize that this approach supports regulatory flexibility, post-approval change management, and strengthening scientific evidence in product development. LSS is not always discussed directly in regulatory language, but it still makes an important contribution to supporting compliance through process standardization, documentation, and better-quality control. Therefore, QbD can be seen as the primary link with regulatory expectations, while LSS serves as an enabler to ensure that such compliance can be achieved efficiently in industry practices.

Results of Syntheses

Based on the comparison table of tools used in selected studies, it can be seen that Quality by Design (QbD) is the most dominant approach in the literature that discusses quality development in the pharmaceutical industry. Studies have indicated that the implementation of QbD consistently utilizes core elements such as Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), design space, control strategy, risk assessment, Design of Experiments (DoE), and Process Analytical Technology (PAT). This pattern shows that QbD not only serves as a conceptual framework, but also as a structured operational approach to build quality from the product and process design stages.

On the other hand, studies focusing on Lean Six Sigma (LSS) emphasize the use of tools that are more oriented towards process efficiency and operational problem-solving. Some of the most commonly used tools include DMAIC, Value Stream Mapping (VSM), Failure Mode and Effects Analysis (FMEA), Statistical Process Control (SPC), fishbone diagram, 5 Whys, Waste Assessment Questionnaire (WAQ), and Waste Relationship Matrix (WRM). The existence of this tool shows that LSS is more directed to identify non-value added activities, reduce waste, reduce variety, and improve process stability in a sustainable manner.

In summary, table 4 shows that QbD and LSS have different but complementary orientations. QbD plays a strong role in establishing scientific foundations, risk-based control, and regulatory compliance, while LSS makes a major contribution to efficiency improvement, waste

elimination, and continuous improvement. Thus, the integration of the two has the potential to produce a more comprehensive quality improvement system in the research and development environment and pharmaceutical manufacturing

Table 3. Characteristics of QbD and Lean Six Sigma Tools

Title and year of publication	Tools related to Quality by Design (QbD)	Tools related to Lean Six Sigma (LSS)
Quality by Design in Pharmaceutical Manufacturing: a systematic review of current status, challenges and future perspectives (Grangeia et al., 2020).	Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), Design Space (DS), Control Strategy, Process Analytical Technology (PAT), Risk Assessment (Ishikawa Diagram, FMEA, Risk Estimation Matrix/REM), Design of Experiments (DoE: 2-level Full/Fractional Factorials, Plackett-Burman, Definitive Screening Designs, Central Composite Design, D-optimal), Multivariate Data Analysis (MVDA: PCA, PLS, O2PLS).	N/A (the study focuses exclusively on QbD methodologies).
Aspects and Implementation of Pharmaceutical Quality by Design from Conceptual Frameworks to Industrial Applications (Yang et al., 2025).	QTPP, CQAs, CMAs, CPPs, Design Space, Control Strategy, Risk Assessment (FMEA, Fault Tree Analysis/FTA, Ishikawa/Fishbone diagrams), DoE, Response Surface Methodology (RSM), PAT (NIR, Raman spectroscopy), Multivariate Analysis (MVA: PLS, PCA, Monte Carlo simulations).	Six Sigma, Plan-Do-Check-Act (PDCA) Cycle, Statistical Process Control (SPC), Control Charts.
Design-for-Six-Sigma for Development of a Bioprocess Quality-by-Design Framework (Junker et al., 2015).	Target Product Profile (TPP), CQAs, Key Process Attributes (KPAs), CPPs, Key Operating Parameters (KOPs), Process Risk Assessment, Design Space, Control Strategy, Continuous Improvement, DoE, Multivariate Data Analysis (MVDA), PAT.	Design-for-Six-Sigma (DFSS), CDOV phases (Concept, Design, Optimize, Verify), Voice-of-the-Customer (VOC) analysis, SWOT analysis, Kano diagram, Affinity diagram, House-of-Quality (HOQ), Quality Function Deployment (QFD), FMEA, Control charts, Statistical Process Control (SPC).
Review on Implementation of Quality by Design (Goswami et al.,	QTPP, Analytical Target Profile (ATP), CQAs, Risk Assessment (Fishbone diagram, FMEA, Ishikawa Diagram), DoE (Plackett-Burman, Fractional	N/A (Study focuses exclusively on QbD).

Title and year of publication	Tools related to Quality by Design (QbD)	Tools related to Lean Six Sigma (LSS)
2024).	Factorial, Central Composite Design, Simplex lattice, Box Behnken), Process Analytical Technology (PAT).	
Applying Lean Six Sigma Methodology to a Pharmaceutical Manufacturing Facility: A Case Study (Byrne et al., 2021a).	N/A (Study focuses exclusively on LSS).	Lean Six Sigma (LSS), DMAIC (Define, Measure, Analyze, Improve, Control) problem-solving cycle, Value Stream Mapping (VSM), Gemba Walk, 5 Whys, Principle of Operation Analysis (POA) / functional analysis diagram, Standard Work, 7-step problem-solving framework.
Lean Six sigma Integration to Reduce Waste in Tablet coating Production with DMAIC and VSM Approach in Production Lines of Manufacturing Companies (Kholil et al., 2021a).	Quality Target Product Profile (QTPP).	Lean Six Sigma, DMAIC, Value Stream Mapping (VSM), VALSAT (Waste Relationship Matrix/WRM, Waste Assessment Questionnaire/WAQ), FMEA, Fishbone/Cause-effect diagram.
Quality by Design (QbD) based process optimisation to develop functionalised particles with modified release properties using novel dry particle coating technique (Dahmash et al., 2018).	QTPP, CQAs, CPPs, Risk Assessment, DoE (using MODDE software, D-optimal design), Response Surface Modelling (RSM), Partial Least Squares (PLS) method.	N/A (Study focuses exclusively on QbD).
Risk and DoE-Based DMAIC Principle to the Multipurpose-RP-HPLC Method for Synchronous Estimation of Anti-Hypertensive Drugs Using AQbD approaches (Prajapati et al., 2021).	Analytical Quality by Design (AQbD), Analytical Target Profile (ATP), Critical Method Performance Attributes (CPAs), Method Operable Design Region (MODR), Risk Assessment (Ishikawa diagram, FMEA / Risk Priority Number/RPN), DoE (Box-Behnken design), Response Surface Analysis, 2D contour plots.	DMAIC principle (integrated as Risk-based DMAIC and DoE-based DMAIC).

Title and year of publication	Tools related to Quality by Design (QbD)	Tools related to Lean Six Sigma (LSS)
A Study on the Build of a QbD Six Sigma System to Promote Quality Improvement(QbD) Based on Drug Design (Kim & Kim, 2022a).	QTPP, CQA, CPP, CMA, Design Space (DS), Control Strategy (CS), Process Analytical Technology (PAT), DoE, Risk Assessment, FMEA (RPN), Fishbone Diagram.	Six Sigma, DMAIC roadmap, Belt certification system (Green Belt, Black Belt, Master Black Belt), Quality Function Deployment (QFD), Measurement System Analysis (MSA), Statistical Process Control (SPC), Capability Analysis (Cp, Z-value), Control Chart, T-Test, ANOVA, Correlation analysis, Regression analysis.

Across all included studies, five primary integration mechanisms emerge that connect QbD with Lean and Six Sigma:

1. Design of Experiments (DoE) Central to both QbD Design Space (DS) establishment and Six Sigma optimization. DoE creates the quantitative and statistical basis for linking Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) to Critical Quality Attributes (CQAs) (al., 2025). Within the integrated framework, DoE is heavily utilized in the 'Improve' phase of the Six Sigma DMAIC cycle to optimize process conditions and systematically establish the multidimensional Design Space.
2. FMEA (Failure Mode and Effects Analysis) Explicitly recommended by the ICH Q9 guideline as a quality risk management tool in QbD, FMEA acts as the most structurally homologous tool shared across both methodologies. It is utilized seamlessly within the 'Analyze' and 'Improve' phases of DMAIC to systematically identify, quantify (via the Risk Priority Number or RPN), and prioritize potential failure modes and their impact on CQAs before establishing a control strategy.
3. Process Capability Analysis (Cp/Cpk) Provides the quantitative link between the statistical evaluation tools of Six Sigma and the quality assurance requirements of a QbD Control Strategy (CS). Process capability metrics (such as targeting a Cpk 1.33) are used to establish a statistical baseline for current performance in the 'Measure' phase, and to continuously confirm that a manufacturing process is capable of performing consistently within its established design space, which is essential for enabling Real-Time Release Testing (RTRT).
4. Value Stream Mapping (VSM) Lean's premier tool for process visualization and flow analysis. Integrated with the DMAIC methodology, VSM is utilized to visually map the "current state" of the manufacturing or development process. It systematically identifies bottlenecks, process downtime, and non-value-adding waste (such as inventory backlogs,

overproduction, or waiting times) so they can be targeted for elimination, ultimately allowing the design of a leaner "future state".

5. DFSS/DMAIC Structure Six Sigma frameworks provide an explicit structural scaffold for executing QbD workflows in a disciplined, data-driven sequence. Design-for-Six-Sigma (DFSS), specifically utilizing CDOV phases (Concept, Design, Optimize, Verify), has been used to systematically construct bioprocess QbD frameworks. Similarly, the DMAIC (Define, Measure, Analyze, Improve, Control) roadmap directly aligns with QbD execution: defining QTPPs/CQAs (Define), assessing current baselines (Measure), identifying CPPs/CMAAs (Analyze), establishing the Design Space via DoE (Improve), and setting the Control Strategy (Control).

Discussion

General Interpretation

A synthesis of the nine articles shows that Quality by Design (QbD) and Six Sigma/Lean Six Sigma (LSS) are not only compatible but have strong methodological alignment. The QbD study places QTPP, CQAs, CMAs, and CPPs as clear starting points, then uses risk assessment (e.g., Ishikawa diagram, FMEA, risk matrix) and DoE to build a robust design space and control strategy. On the other hand, Six Sigma and LSS studies start from the formulation of project problems and goals, then apply the DMAIC, FMEA, capability/performance metrics, and SPC frameworks to reduce variation and improve process performance (Byrne et al., 2021a; Dahmash et al., 2018; Goswami et al., 2024; Grangeia et al., 2020; Hee, 2022; Kholil et al., 2021a; Prajapati et al., 2021; Yang et al., 2025).

Some articles explicitly combine the two approaches at the method level. DFSS is used to design a bioprocess QbD framework in the vaccine and biologics industry; AQbD is combined with DMAIC and Box–Behnken DoE to develop a multipurpose RP-HPLC method; and a QbD Six Sigma system is proposed to strengthen QbD execution through a Six Sigma belt structure and strengthen statistical competencies in pharmaceutical organizations. This shows that QbD provides a scientific and regulatory architecture, while Six Sigma provides a problem-solving and statistical discipline that is compatible with QbD principles (Hee, 2022; Junker et al., 2015; Prajapati et al., 2021).

The role of Lean appears to be dominant in studies that focus on improving the efficiency of manufacturing processes. Lean Six Sigma is used to map value streams, identify waste (overproduction, defects, and inventory), and design improvements to reduce downtime, backlog, and reject rates in paracetamol and tablet coating packaging lines. Although the context of both studies is manufacturing, the patterns of improvement, like reduced wait times, reduction of non-value-added activities, and improvement of process flow, are conceptually relevant to R&D, especially when QbD demands repetitive, intensive experimentation cycles (Byrne et al., 2021a; Kholil et al., 2021a).

Analytical Comparison of Integration Models

Based on nine studies, at least three patterns of integration can be identified. The first model is a sequential integration based on QbD–Six Sigma, where QbD defines quality goals and design space, while Six Sigma (DFSS or DMAIC) provides a structured execution path. This approach is evident in the DFSS article that develops the QbD framework for bioprocesses, where QbD needs are translated into the DFSS (charter, design, risk evaluation, and implementation plan) stages. A similar pattern is also seen in the AQbD–DMAIC method for RP-HPLC, where ATP and CPAs are defined by the principle of QbD, then optimized with DMAIC and DoE (Junker et al., 2015; Prajapati et al., 2021).

The second model is tool-level integration. A number of QbD studies use FMEA, Ishikawa diagrams, and DoE to manage risk and process optimization without explicitly mentioning Six Sigma, while LSS studies utilize FMEA, statistical analysis, and in some cases trial design to identify and reduce the causes of waste. Thus, there is an overlap of tools and principles, especially in risk assessment and DoE, although integration is not always packaged as a single formal framework (Byrne et al., 2021a; Dahmash et al., 2018; Goswami et al., 2024; Grangeia et al., 2020; Kholil et al., 2021a; Yang et al., 2025)

The third model is integration at the management system level (operational excellence integration). Lean Six Sigma study at paracetamol facilities and PT. Medica Indonesia shows that LSS functions as a continuous repair management system to reduce defects, downtime, and inventory through DMAIC, VSM, VALSAT, and FMEA. On the other hand, Kim & Kim's proposed Six Sigma QbD system positions QbD as the design base and Six Sigma as a quality management system that builds statistical capabilities, belt structures, and a culture of continuous improvement in the organization.

Although this model has not been fully tested in the context of end-to-end R&D, it indicates the potential of QbD as "content" and LSS as a "system" within the framework of pharmaceutical operational excellence (Byrne et al., 2021b; Kholil et al., 2021b; Kim & Kim, 2022b).

Identification of Research Gaps

An analysis of the nine articles revealed several research gaps. First, there has not been a single study that has proposed and empirically tested an integrated QbD–Lean–LSS framework from upstream to downstream for the entire pharmaceutical R&D cycle. QbD studies tend to focus on product development and analytical processes or methods, while LSS studies are more focused on improving manufacturing processes or specific improvement cases.

Second, the empirical evidence for integration comes more from the manufacturing context than from R&D. Lean Six Sigma studies in tablet coating and packaging show a clear impact on waste and efficiency, while QbD evidence in the R&D area is more in the form of conceptual reviews and process optimization studies at laboratory scale or the development of analytical methods. This suggests that integrated applications in more exploratory R&D environments are still relatively poorly documented.

Third, no studies were found that directly compared project outcomes (e.g., development cycle time, first-pass success rate, or quality of regulatory documents) between organizations that

implemented QbD only, LSS only, and integrated QbD–LSS. Existing studies report on the benefits of each approach—such as reduced batch failures and waste in QbD, as well as financial savings and reduced downtime in LSS, but have not provided a quantitative comparison between integration and non-integration models. Fourth, the new organizational and cultural dimensions are explicitly touched on the Six Sigma QbD system, which emphasizes the role of statistical education, the belt system, and strengthening the execution of Six Sigma-based QbD. Most of the other articles focus more on technical tools and methodological aspects, so factors such as leadership, cross-functional organizational structure, and change management have not been explored in depth.

Fifth, integration with new cutting-edge technologies is comprehensively discussed in the *Pharmaceutics 2025* review, which highlights the potential of combining QbD with PAT, multivariate data analysis, predictive models, and even AI-based approaches to process development and control. Dry particle coating-based QbD studies have also demonstrated the use of advanced DoE software and multivariate analysis to build predictive models, but have not explicitly linked them to Lean or Six Sigma. Thus, the research space in the QbD–LSS–digital technology slice is still wide open.

CONCLUSION

A review of the nine selected articles demonstrates that Quality by Design (QbD), Lean, and Six Sigma have complementary methodological foundations and can theoretically be integrated into a coherent operational excellence system for the pharmaceutical industry. QbD provides a scientific and regulatory framework based on Quality Target Product Profiles (QTPPs), Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), design space, and quality risk management. Six Sigma provides structured statistical and problem-solving frameworks through Design for Six Sigma (DFSS), Define, Measure, Analyze, Improve, and Control (DMAIC), Failure Mode and Effects Analysis (FMEA), process capability analysis, and Statistical Process Control (SPC). Lean, particularly when integrated with Six Sigma as Lean Six Sigma (LSS), focuses on waste reduction, process flow improvement, and cycle-time reduction, as demonstrated in studies involving tablet coating and packaging.

Although the potential for synergy is evident, the existing literature has not yet presented a validated, end-to-end integration framework encompassing the entire pharmaceutical R&D and manufacturing lifecycle. Existing studies still tend to examine QbD and LSS separately or integrate them only within specific areas, such as analytical method development or individual manufacturing processes. Therefore, a key opportunity for future research is to design, implement, and validate a comprehensive QbD–Lean Six Sigma framework that enables pharmaceutical organizations to move beyond partial and fragmented implementation. Successful development and implementation of such a framework could contribute directly to more efficient pharmaceutical development and manufacturing processes, shorter development timelines, improved product quality and process robustness, and ultimately the delivery of safe, effective, and high-quality drug products to patients.

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