Review article

Modern approaches to pharmaceutical manufacturing optimization: integrating Lean, QbD, PAT and Pharma 4.0 into the pharmaceutical quality system

Kuzmina V.V.[1], Kuzmina R.V.[1], Kizatova M.Zh.[1], Rakhimova N.A.[1], Sharipova O.F.[1]*

[1] S.D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

* Corresponding author: Olga F. Sharipova · sharipova.o@kaznmu.kz

Volume 1 · Issue 1 · 2026 | Received: July 2026 | Published: 29 September 2026

Abstract

The aim of this narrative review was to compare current approaches to pharmaceutical manufacturing optimization and to define their roles within the pharmaceutical quality system. Relevant scientific publications and regulatory documents were reviewed in PubMed, Scopus and Web of Science and supplemented with regulatory documents from ICH, FDA, WHO, PIC/S and the European Commission; the last search was conducted on 28 September 2026. Peer-reviewed publications from 2015-2026 were prioritized, while earlier sources were retained when they represented foundational or regulatory documents. The approaches were compared by management object, lifecycle stage, data requirements, performance indicators and limitations. Lean primarily addresses process flow and waste, Six Sigma focuses on variability, QbD on product and process design, PAT and continued process verification on monitoring and maintenance of a state of control, and Pharma 4.0 on data and system integration. These approaches should not be interpreted as a mandatory linear sequence. Their combination depends on process knowledge, data quality, regulatory constraints and the digital maturity of the manufacturing site. A comparative analytical model is proposed to position the reviewed tools within the pharmaceutical quality system.

Keywords: pharmaceutical manufacturing; pharmaceutical quality system; Lean; Six Sigma; Quality by Design; Process Analytical Technology; continued process verification; continuous manufacturing; Pharma 4.0; quality management maturity.

To cite this article: Kuzmina V.V., Kuzmina R.V., Kizatova M.Zh., Rakhimova N.A., Sharipova O.F. Modern approaches to pharmaceutical manufacturing optimization: integrating Lean, QbD, PAT and Pharma 4.0 into the pharmaceutical quality system. Pharmaceutical Sciences and Health Products. 2026;1(1):e0001.

Introduction

Pharmaceutical manufacturing is an industry in which efficiency improvements cannot be considered separately from quality assurance. Reductions in cycle time or production waste are meaningful only if the validated state of the process is maintained, risks are managed and good manufacturing practice requirements are met. ICH Q8-Q10 and the modern approach to process validation regard quality as the outcome of process design, understanding and control throughout the lifecycle [1-3, 6].

Over the past two decades, Lean and Six Sigma, Quality by Design (QbD), Process Analytical Technology (PAT), continued process verification (CPV), continuous manufacturing, quality-system maturity tools and Pharma 4.0 digital solutions have become established simultaneously at manufacturing sites [5, 18, 29, 34, 38]. These areas are often discussed separately in the literature, making their boundaries and complementary roles difficult to understand. For example, Lean and Six Sigma mainly address operational and statistical problems, whereas QbD concerns scientifically grounded product and process design; digital infrastructure alone replaces neither a control strategy nor a pharmaceutical quality system.

A separate issue concerns the term “stability”. In this review, process stability means the ability of a process to maintain a controlled and reproducible state within established variability. This concept is not equivalent to sustainable development in the environmental and ESG context. Environmental indicators, resource conservation and carbon footprint therefore fall outside the scope of this review.

A single analytical framework was used to compare these heterogeneous approaches: object of management, tools, indicators, limitations and position within the pharmaceutical quality system.

The aim was to define the functional boundaries and conditions for combining current approaches to pharmaceutical manufacturing optimization without artificially reducing them to a single universal sequence.

Materials and methods

This study was conducted as a narrative review. This format was chosen because of the heterogeneity of the subjects considered: regulatory concepts, process improvement methods, statistical tools and digital technologies were compared within a single analytical framework. Quantitative pooling and meta-analysis were not performed.

Scientific publications were searched in PubMed, Scopus and Web of Science; regulatory and methodological documents were checked against the official resources of ICH, FDA, WHO, PIC/S and the European Commission. The last search was performed on 28 September 2026. The main search period was 2015-2026. Earlier publications were included only when they were foundational to the concept under consideration or retained regulatory relevance.

Combinations of terms with AND/OR operators were used, including: “pharmaceutical manufacturing” AND (“process optimization” OR “operational excellence”); (“Quality by Design” OR QbD) AND (PAT OR “continued process verification”); “continuous manufacturing” AND (“residence time distribution” OR traceability OR “diversion strategy”); (“Pharma 4.0” OR “Industry 4.0”) AND (“data integrity” OR cybersecurity OR interoperability); (“quality management maturity” OR “quality culture”) AND pharmaceutical. Titles, abstracts and keywords were searched where the database allowed these fields to be specified.

The synthesis was qualitative and comparative. For each approach, the main object of management, types of tools, position in the product and process lifecycle, performance indicators, data requirements and limitations were assessed. An author-developed comparative matrix was constructed on this basis and is presented in Table 1.

The process approach and the pharmaceutical quality system

The process approach establishes the overall logic of management: quality is viewed as the outcome of relationships among inputs, material attributes, technological operations, process parameters and the decision-making system. In the pharmaceutical setting, this logic is established in ICH Q10 and is consistent with the general principles of quality management systems [3, 15]. Control therefore concerns not only finished-product compliance with specifications but also the ability of the process to deliver the required outcome consistently.

Several levels should be distinguished for practical management. Product and process knowledge is generated during development; established parameters and the control strategy are maintained at the manufacturing level; and trends, deviations, CAPA, changes and audit outcomes are analysed at the quality-system level. This distinction prevents duplication between the process approach and individual tools such as QbD, PAT or CPV: the process approach provides the framework, while these concepts perform specific functions within it [1-3].

Internal audit should not be interpreted as an independent optimization tool within this system. Its purpose is to obtain independent evidence that processes and quality-system elements comply with established requirements and remain effective. Audit planning and execution should be aligned with ISO 19011, GMP self-inspection requirements and ICH Q10 principles [3, 12, 14]. Audit findings may inform improvement activities, but they do not in themselves

demonstrate the effectiveness of a particular optimization method.

Lean and Six Sigma: process flow and variability management

Lean focuses on identifying activities that do not add value and reducing waiting, unnecessary movement, excess inventory and other forms of waste. This has additional importance for pharmaceutical manufacturers: delays in batch release, complex documentation workflows and lengthy changeovers can extend cycle times while creating organizational conditions for errors. Common tools include Value Stream Mapping, 5S, standardized work, SMED and elements of total productive maintenance [29, 30].

Transferring Lean results between manufacturing sites requires caution. The effect depends on product type, process scale, automation level and the initial organization of production; universal percentages for cycle-time reduction are therefore not appropriate indicators. Pharmaceutical case studies show that Lean and operational excellence approaches can improve equipment availability and maintenance arrangements, but findings from individual sites cannot automatically be extrapolated to the industry as a whole [29].

Six Sigma complements Lean with statistical reasoning. The DMAIC cycle (Define-Measure-Analyze-Improve-Control) is used to define a problem, measure the baseline, analyse causes of variability, implement changes and maintain subsequent control [31]. Control charts, process capability indices Cp/Cpk, regression models and design of experiments distinguish common-cause variation from special causes and enable quantitative assessment of the process state [21, 22].

Lean and Six Sigma should be regarded as complementary rather than interchangeable approaches. Lean is better suited to identifying waste and flow problems, whereas Six Sigma requires sufficient reliable data and is appropriate when quantitative assessment of variability is important. Their combined use is most meaningful after a specific manufacturing problem has been identified, rather than as a formal programme applied uniformly to all areas [29-31].

Quality by Design, PAT and continued process verification

Quality by Design provides the scientific foundation for development: the quality target product profile (QTPP) is linked to critical quality attributes (CQA), critical material attributes (CMA) and critical process parameters (CPP). Risk analysis and design of experiments identify significant factors, their interactions (Figure 1) and ranges within which the required quality is achieved [1, 16-21]. The systematic review by Grangeia et al. shows that FMEA and various DoE approaches are particularly common in practical QbD studies, although implementation in routine commercial manufacturing remains uneven [18].

In regulatory terms, PAT is a system for designing, analysing and controlling manufacturing through timely measurement of critical attributes of materials, intermediate products and processes. PAT should therefore not be reduced to the presence of a sensor or a rapid laboratory method. An analytical tool becomes part of PAT only within a defined control strategy, data interpretation model and decision rules [7]. NIR and Raman spectroscopy are typical technologies that can monitor moisture, blend uniformity or other attributes without destructive sampling [23, 24].

Continued process verification is the third stage of the process validation lifecycle and involves collecting and analysing data during commercial manufacturing to confirm that the process remains in a state of control [6]. It is a continuation of the lifecycle approach rather than an alternative to “one-off traditional validation”: knowledge generated during development and process qualification is tested and refined using batch data, trends and changes (Figure 2).

The relationship between QbD, PAT and CPV is functional rather than linear. QbD can be implemented without sophisticated on-line analytics; PAT can form part of the control strategy in both batch and continuous manufacturing; and PAT data can in turn be used in CPV. Thus, “QbD → PAT → CPV” is useful as an illustration of their relationship but should not be interpreted as a mandatory implementation sequence [1, 6, 7].

Continuous manufacturing and process control

Continuous manufacturing involves the continuous feeding and transformation of materials and removal of product within an integrated technological system. Continuous operation does not eliminate the batch concept: ICH Q13 provides for a regulatory justification of batch or lot definition based on the quantity of material produced, production time or other established criteria [5].

A key challenge in a continuous process is material traceability. Residence time distribution (RTD) is used to assess the propagation of material and disturbances along the line, identify transition zones and justify decisions to

direct product into the main stream or divert it. Reviews and experimental studies demonstrate the practical role of RTD during raw-material lot changes and identification of transient states [25, 26].

A continuous manufacturing control strategy must account for start-up and shutdown, feed deviations, material accumulation, traceability, PAT and rules for managing nonconforming streams [5, 27, 28]. Here, active process control means automated corrective action on the technological process based on measured parameters and predefined control rules. This may involve feedback and feed-forward loops, model predictive control or other algorithms that adjust the process according to measured parameters. Such systems differ from real-time release testing: automated process regulation and decisions on product release are related but distinct tasks.

Potential benefits of continuous manufacturing include reduced intermediate inventories, flexible scaling and closer integration of control with the process. Limitations include the need for stable feeder and analytical-system operation, appropriate RTD modelling, algorithm qualification, data governance and staff training. Selection of a continuous configuration should therefore be based on the properties of the particular product and process rather than a general assumption of its superiority [5, 25-28].

Quality-system maturity, quality culture, deviations and CAPA

Organizational factors determine how well technical tools work in actual manufacturing. ICH Q10 links the pharmaceutical quality system to management responsibility, knowledge management, risk management, CAPA, change management and management review [3]. Quality Management Maturity (QMM) develops this logic further: attention shifts from the mere existence of procedures to the organization's ability to identify risks consistently, use data and sustain continual improvement [34-36].

Empirical studies of quality culture indicate associations between behavioural and organizational characteristics and quality-system maturity, although culture itself remains difficult to measure [32, 33]. It is therefore more appropriate to assess it through a set of features-management involvement, transparency in deviation reporting, improvement objectives, cross-functional analysis, feedback and the use of indicators-rather than a single aggregate score. More recent studies also propose structured indicators of quality culture, confirming the continuing development of the methodology [42].

Deviation management and CAPA serve as feedback mechanisms in this system. Not only investigation closure times matter, but also the quality of root-cause analysis, the justification of actions and verification of their effectiveness. Recurrent similar deviations may signal that actions are insufficiently effective, but do not by themselves justify describing a quality system as weak without contextual analysis. Audits should assess trends, investigation quality, timeliness and demonstrated CAPA effectiveness alongside other quality-system data [3, 12, 14].

Evidence from FDA QMM programmes and industry studies also links quality maturity to the resilience of manufacturing performance and supply chains [34-37]. However, these observations do not justify ranking sites or optimization methods outside a defined assessment methodology. In this review, QMM is viewed as an organizational layer that determines a manufacturer's ability to sustain technical improvements and use their outcomes.

Digitalization and Pharma 4.0: data as quality infrastructure

In manufacturing, digitization of individual data, digitalization of processes and Pharma 4.0 should be distinguished. Digitization converts information into digital form; digitalization uses digital data to execute and manage processes; Pharma 4.0 entails deeper integration of equipment, information systems, analytics and organizational processes within a common architecture [38]. Automation may therefore be part of digitalization but is not synonymous with it.

Technologies that may be used in Pharma 4.0 include MES, electronic batch records, LIMS, industrial IoT devices, cloud analytics, digital twins and artificial intelligence algorithms. Practical studies demonstrate the feasibility of combining data streams from continuous pilot lines and models in a shared information environment [39]. The value of such solutions, however, depends on data quality, context and the traceability of information provenance and transformation rather than the number of digital components.

Data integrity remains a central constraint of the digital model. ALCOA+ requirements and regulatory expectations encompass attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available data. Reviews of inspection observations show that data-integrity failures can arise in procedures as well as in system configuration and access management [10, 40]. Computerized systems additionally require lifecycle management, validation, segregation of access rights, audit trails, backups and change management [13].

As systems become integrated, interoperability and cybersecurity grow in importance. Connecting legacy equipment, laboratory systems and manufacturing platforms requires standardized interfaces and consistent data semantics, while connectivity expands the cyber-risk surface. Studies of manufacturing-data architecture and information exchange highlight the potential of standardized

interfaces while emphasizing access control, algorithm verification and change management [39, 41].

Artificial intelligence and predictive analytics are appropriate where sufficient representative data exist and the task has been predefined, such as anomaly detection, predictive maintenance, trend analysis or decision support. A model must not replace pharmaceutical judgement or the established risk management system. Regulated manufacturing requires validation of input data, traceability of model versions, acceptance criteria and change control. Pharma 4.0 should therefore be viewed as a digital layer of the pharmaceutical quality system rather than an autonomous management concept.

A comparative model for integrating the approaches

Comparison shows that the approaches operate at different levels and answer different management questions. Table 1 was developed by the authors from this review; no numerical ranking of methods was performed because the underlying studies differ in their subjects, designs and performance indicators.

Abbreviations: VSM, Value Stream Mapping; WIP, Work in Process; OEE, Overall Equipment Effectiveness; DMAIC, Define-Measure-Analyze-Improve-Control; SPC, Statistical Process Control; Cp/Cpk, process capability indices; DoE, Design of Experiments; QTPP, Quality Target Product Profile; CQA, Critical Quality Attributes; CMA, Critical Material Attributes; CPP, Critical Process Parameters; NIR, Near-Infrared Spectroscopy; RTRT, Real-Time Release Testing; RTD, Residence Time Distribution; QMM, Quality Management Maturity; PQS, Pharmaceutical Quality System; CAPA, Corrective and Preventive Actions; MES, Manufacturing Execution System; eBR, electronic Batch Record; LIMS, Laboratory Information Management System; IIoT, Industrial Internet of Things; AI/ML, Artificial Intelligence/Machine Learning; API, Application Programming Interface.

The comparative model does not imply that a manufacturer should implement all approaches simultaneously. QbD and risk management may take priority during development; SPC, CPV and targeted Lean/Six Sigma projects may be more relevant to an established process; and RTD, PAT and automated control gain importance when moving to continuous manufacturing. Pharma 4.0 provides infrastructure for combining these data, but its effectiveness depends on pharmaceutical quality-system maturity.

In practical terms, integration is appropriate when a clear causal relationship exists between a tool and the manufacturing problem. For example, an increase in batch-release time should not automatically be addressed with a digital platform: first, it is necessary to establish whether the delay results from waiting for quality-control results, changeovers, documentation or process variability. Only then should the appropriate tool and outcome indicator be selected.

Limitations of the review

This is a narrative rather than a systematic review. It does not include meta-analysis and cannot quantitatively rank the approaches by effectiveness. Sources range from regulatory documents and methodological guidance to reviews and individual manufacturing case studies, limiting direct comparison of numerical results. Several concepts are also evolving rapidly, particularly in Pharma 4.0, data governance and digital algorithms; individual technological solutions may change faster than regulatory practice. The conclusions should be regarded as an analytical framework for selecting and combining tools rather than a universal implementation algorithm.

Conclusion

Pharmaceutical manufacturing optimization comprises tasks at different levels; reducing Lean, Six Sigma, QbD, PAT, CPV, continuous manufacturing and Pharma 4.0 to a single sequential scheme is therefore methodologically unjustified. Lean and Six Sigma mainly address operational flow and variability; QbD generates knowledge and a control strategy; PAT and CPV support process monitoring and confirmation of the state of control; continuous manufacturing requires a specific architecture for traceability and material management; QMM and quality culture determine organizational capacity to sustain improvements; and Pharma 4.0 enables digital data integration.

Combined use of these approaches is justified when three conditions are met: a clearly defined manufacturing problem, reliable data and a mature pharmaceutical quality system. These conditions, rather than the number of tools implemented, determine the practical value of optimization. The proposed comparative matrix can support method selection for a particular lifecycle stage and planning of internal audits, CAPA and continual improvement programmes.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Kuzmina V. V., Kuzmina R. V., Kizatova M. Zh., Rakhimova N. A. and Sharipova O. F.: study conception, development of the review methodology, literature search and analysis, interpretation of findings, drafting of the manuscript, critical revision and approval of the final version.

All authors have read and agreed to the final version of the manuscript. The authors state that this material has not

been published previously and is not under consideration by other publishers.

Funding

The study received no external funding.

Data availability statement

This work is a narrative literature review. No new clinical or experimental quantitative data were collected. The materials used for analysis and formulation of the conclusions are available in the cited references.

Author information

Kuzmina V. V. - 2nd-year master's student in the Pharmacy educational program, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. E-mail: woody.adolescent@gmail.com. ORCID: https://orcid.org/0009-0003-5656-0568.

Kuzmina R. V. - 2nd-year master's student in the Pharmacy educational program, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. E-mail: kruslana20031411@gmail.com. ORCID: https://orcid.org/0009-0001-5559-0226.

Kizatova M. Zh. - Doctor of Technical Sciences, Professor of the Department of Pharmaceutical Technology, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. E-mail: kizatova@mail.ru. ORCID: https://orcid.org/0000-0002-6481-7410.

Rakhimova N. A. - 3rd-year PhD student in the 8D10102 Pharmacy educational program, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. E-mail: nargiz02@inbox.ru. ORCID: https://orcid.org/0000-0003-4950-9951.

Sharipova Olga Fridovna - Researcher at the Center for Pharmacy and Pharmacology, Science and Technology Park, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. E-mail: sharipova.o@kaznmu.kz. ORCID: https://orcid.org/0009-0006-9829-0991.

References

1. ICH. Q8(R2) Pharmaceutical Development. Geneva: International Council for Harmonisation; 2009.

2. ICH. Q9(R1) Quality Risk Management. Geneva: International Council for Harmonisation; 2023.

3. ICH. Q10 Pharmaceutical Quality System. Geneva: International Council for Harmonisation; 2008.

4. ICH. Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. Geneva: International Council for Harmonisation; 2019.

5. ICH. Q13 Continuous Manufacturing of Drug Substances and Drug Products. Geneva: International Council for Harmonisation; 2022.

6. U.S. Food and Drug Administration. Process Validation: General Principles and Practices. Guidance for Industry. Silver Spring, MD: FDA; 2011.

7. U.S. Food and Drug Administration. PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Guidance for Industry. Silver Spring, MD: FDA; 2004.

8. World Health Organization. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Technical Report Series No. 986, Annex 2. Geneva: WHO; 2014.

9. PIC/S. Guide to Good Manufacturing Practice for Medicinal Products, PE 009-18. Geneva: Pharmaceutical Inspection Co-operation Scheme; 2026.

10. PIC/S. Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments, PI 041-1. Geneva: Pharmaceutical Inspection Co-operation Scheme; 2021.

11. European Commission. EudraLex, Volume 4, Part I, Chapter 1: Pharmaceutical Quality System. Brussels: European Commission; 2013.

12. European Commission. EudraLex, Volume 4, Part I, Chapter 9: Self Inspection. Brussels: European Commission. Accessed September 28, 2026.

13. European Commission. EudraLex, Volume 4, Annex 11: Computerised Systems. Brussels: European Commission; 2011.

14. ISO. ISO 19011:2026. Guidelines for auditing management systems. Geneva: International Organization for Standardization; 2026.

15. ISO. ISO 9001:2026. Quality management systems - Requirements. Geneva: International Organization for Standardization; 2026.

16. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008;25(4):781-791. doi:10.1007/s11095-007-9511-1.

17. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771-783. doi:10.1208/s12248-014-9598-3.

18. Grangeia HB, Silva C, Simões SP, Reis MS. Quality by design in pharmaceutical manufacturing: a systematic review of current status, challenges and future perspectives. Eur J Pharm Biopharm. 2020;147:19-37. doi:10.1016/j.ejpb.2019.12.007.

19. Pramod K, Tahir MA, Charoo NA, Ansari SH, Ali J. Pharmaceutical product development: a quality by design approach. Int J Pharm Investig. 2016;6(3):129-138. doi:10.4103/2230-973X.187350.

20. Aksu B, Paradkar A, de Matas M, Ozer O, Güneri T, York P. Quality by design approach: application of artificial intelligence techniques of tablets manufactured by direct compression. AAPS PharmSciTech. 2012;13(4):1138-1146. doi:10.1208/s12249-012-9836-x.

21. Montgomery DC. Design and Analysis of Experiments. 9th ed. Hoboken, NJ: John Wiley & Sons; 2017.

22. Montgomery DC. Introduction to Statistical Quality Control. 8th ed. Hoboken, NJ: John Wiley & Sons; 2020.

23. De Beer T, Burggraeve A, Fonteyne M, Saerens L, Remon JP, Vervaet C. Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. Int J Pharm. 2011;417(1-2):32-47. doi:10.1016/j.ijpharm.2010.12.012.

24. Fonteyne M, Vercruysse J, De Leersnyder F, Van Snick B, Vervaet C, Remon JP, et al. Process analytical technology for continuous manufacturing of solid-dosage forms. TrAC Trends Anal Chem. 2015;67:159-166. doi:10.1016/j.trac.2015.01.011.

25. Bhalode P, Tian H, Gupta S, Razavi SM, Roman-Ospino A, Talebian S, et al. Using residence time distribution in pharmaceutical solid dose manufacturing - a critical review. Int J Pharm. 2021;610:121248. doi:10.1016/j.ijpharm.2021.121248.

26. Sánchez-Paternina A, Martínez-Cartagena P, Li J, Scicolone JV, Singh R, Lugo YC, et al. Residence time distribution as a traceability method for lot changes in a pharmaceutical continuous manufacturing system. Int J Pharm. 2022;611:121313.

doi:10.1016/j.ijpharm.2021.121313.

27. Ierapetritou M, Muzzio F, Reklaitis G. Perspectives on the continuous manufacturing of powder-based pharmaceutical processes. AIChE J. 2016;62(6):1846-1862. doi:10.1002/aic.15210.

28. Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD, et al. Modernizing pharmaceutical manufacturing: from batch to continuous production. J Pharm Innov. 2015;10(3):191-199. doi:10.1007/s12247-015-9215-8.

29. Shannon N, Trubetskaya A, Iqbal J, McDermott O. A total productive maintenance & reliability framework for an active pharmaceutical ingredient plant utilising design for Lean Six Sigma. Heliyon. 2023;9(10):e20516. doi:10.1016/j.heliyon.2023.e20516.

30. Shah R, Ward PT. Lean manufacturing: context, practice bundles, and performance. J Oper Manag. 2003;21(2):129-149. doi:10.1016/S0272-6963(02)00108-0.

31. Antony J, Bañuelas R. Key ingredients for the effective implementation of Six Sigma program. Meas Bus Excell. 2002;6(4):20-27. doi:10.1108/13683040210451679.

32. Patel P, Baker D, Burdick R, Chen C, Hill J, Holland M, et al. Quality Culture Survey Report. PDA J Pharm Sci Technol. 2015;69(5):631-642. doi:10.5731/pdajpst.2015.01078.

33. Friedli T, Buess P, Köhler S, Chen C, Mendivil S, Baker D. The impact of quality culture on operational performance - an empirical study from the pharmaceutical industry. PDA J Pharm Sci Technol. 2018;72(5):531-542. doi:10.5731/pdajpst.2018.008771.

34. Fellows M, Friedli T, Li Y, Maguire J, Rakala N, Ritz M, et al. Benchmarking the quality practices of global pharmaceutical manufacturing to advance supply chain resilience. AAPS J. 2022;24(6):111. doi:10.1208/s12248-022-00761-7.

35. Maguire J, Fisher A, Harouaka D, Rakala N, Lundi C, Yambot M, et al. Lessons from CDER's Quality Management Maturity Pilot Programs. AAPS J. 2023;25(1):14. doi:10.1208/s12248-022-00777-z.

36. U.S. Food and Drug Administration. CDER's Quality Management Maturity (QMM) Program: Practice Areas and Prototype Assessment Protocol Development. White Paper. Silver Spring, MD: FDA; 2023.

37. U.S. Food and Drug Administration. Drug Shortages: Root Causes and Potential Solutions. Report by the Drug Shortages Task Force. Silver Spring, MD: FDA; 2019; updated 2020.

38. Arden NS, Fisher AC, Tyner K, Yu LX, Lee SL, Kopcha M. Industry 4.0 for pharmaceutical manufacturing: preparing for the smart factories of the future. Int J Pharm. 2021;602:120554. doi:10.1016/j.ijpharm.2021.120554.

39. Chen Y, Sampat C, Huang YS, Ganesh S, Singh R, Ramachandran R, et al. An integrated data management and informatics framework for continuous drug product manufacturing processes: a case study on two pilot plants. Int J Pharm. 2023;642:123086. doi:10.1016/j.ijpharm.2023.123086.

40. Charoo NA, Khan MA, Rahman Z. Data integrity issues in pharmaceutical industry: common observations, challenges and mitigations strategies. Int J Pharm. 2023;631:122503. doi:10.1016/j.ijpharm.2022.122503.

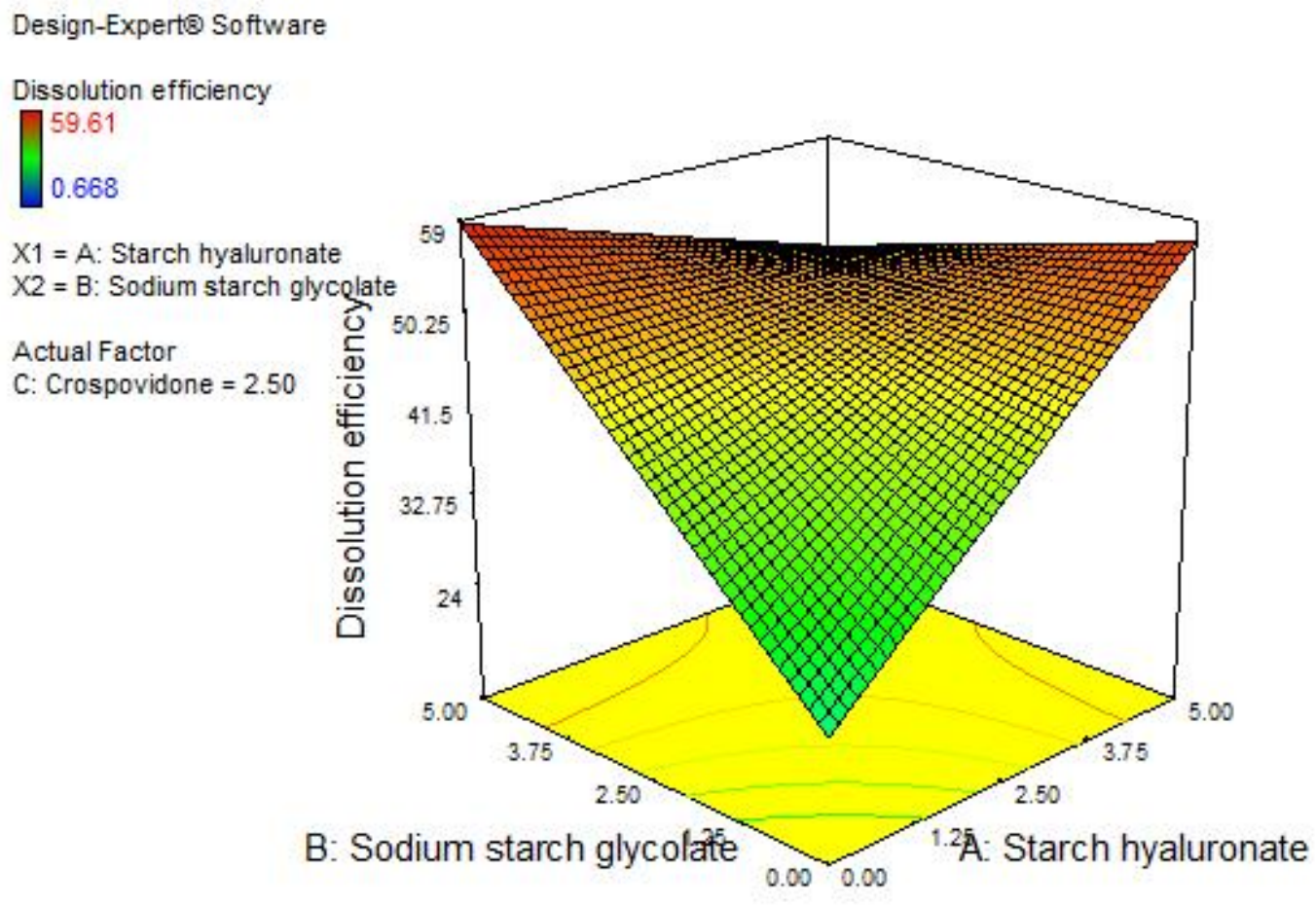
41. Anderson C, Algorri M, Abernathy MJ. Real-time algorithmic exchange and processing of pharmaceutical quality data and information. Int J Pharm. 2023;645:123342. doi:10.1016/j.ijpharm.2023.123342.

42. Takahashi S, Takarada T, Kitamura R, Shikano M, Sakurai S. Creating an assessment indicator of quality culture development in the generic pharmaceutical industry in Japan. PDA J Pharm Sci Technol. 2024;78(1):45-69. doi:10.5731/pdajpst.2022.012824.

43. Ng Corrales LDC, Lambán MP, Hernandez Korner ME, Royo J. Overall Equipment Effectiveness: systematic literature review and overview of different approaches. Appl Sci. 2020;10(18):6469. doi:10.3390/app10186469.

44. Kusuma A, Kumar R S. Optimization of fast-dissolving tablets of carvedilol using 2^3 factorial design. Int J App Pharm. 2024;16(1):98-107. doi:10.22159/ijap.2024v16i1.49535.

Figure 1. Three-dimensional response surface with contour projection obtained by Design of Experiments (DoE), illustrating the combined effect of two factors on a quality attribute [44].



Source: Kusuma A., Kumar R. S. (2024), Figure 13, right panel [44]. DOI: 10.22159/ijap.2024v16i1.49535. CC BY 4.0. Reproduced from the supplied manuscript; data are unchanged.

Figure 2. Example of a Process Capability Sixpack report assessing process stability and capability for rotational speed (prepared by the authors).

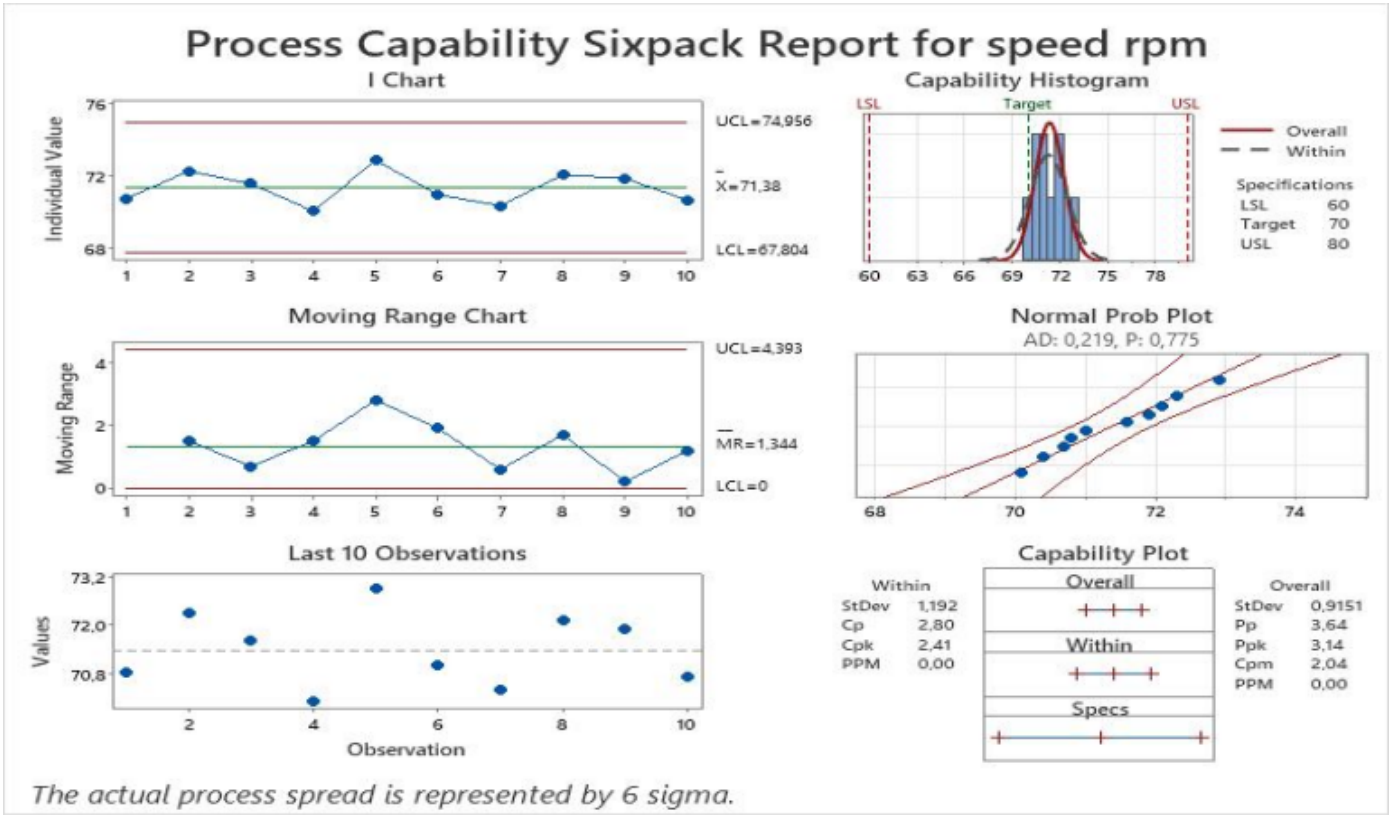


Figure supplied by the authors. Original statistical notation and numerical values are preserved.

Table 1. Comparison of approaches to pharmaceutical manufacturing optimization.

Approach	Main aim	Object of management	Key tools	Indicators / data	Main limitations	Role within the pharmaceutical quality system
Lean	Reduce waste and organize flow	Sequence of operations, waiting, inventory, changeovers	VSM, 5S, SMED, standardized work [29, 30]	Lead time, WIP, changeover time, OEE	Not primarily designed for quantitative statistical assessment of variability; effects depend on the initial process	Operational efficiency and flow organization
Six Sigma	Reduce variability and defects	Process parameters and outcomes	DMAIC, SPC, Cp/Cpk, regression, DoE	Variability, process capability, defect frequency	Requires sufficient, valid data; sensitive to problem definition	Statistically grounded process improvement
QbD	Design quality and understand the process	QTPP, CQA, CMA, CPP	Risk management, DoE, design space, control strategy	Factor-response relationships, parameter ranges, risks	Resource-intensive development; experimental data required	Development and knowledge management throughout the lifecycle
PAT	Timely measurement and control support	Critical material and process attributes	NIR, Raman, chemometrics, process analysers	Trends, CQA/CPP proxies, models	Model calibration and maintenance; equipment integration	Monitoring and an element of the control strategy; support for RTRT when justified
CPV	Confirm the state of control in commercial manufacturing	Long-term stability of the validated process	Trending, SPC, batch and deviation analysis	Drift, variability, process capability	Depends on data quality and comparability	Third stage of lifecycle process validation
Continuous manufacturing	Integrated flow and material control	Material flow and transient states	RTD, PAT, feeder control, diversion strategy	RTD, mass balance, transition parameters, yield	Traceability, start-up/shutdown, batch definition, control complexity	Manufacturing architecture and control strategy
QMM / quality culture	Increase organizational maturity and proactivity	Management, behaviour, PQS processes	Management review, metrics, CAPA, audit, improvement systems	Recurrent deviations, CAPA effectiveness, quality metrics	Difficulties in standardized culture assessment; context dependence	Organizational foundation of PQS effectiveness
Pharma 4.0	Integrate data and provide digital decision support	Data, information and cyber-physical systems	MES, eBR, LIMS, IIoT, AI/ML, digital twin, API	Data completeness and timeliness, latency, predictive performance	Data integrity, cybersecurity, interoperability, validation	Digital layer connecting manufacturing and the quality system