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Quality by Design (QbD) in Novel Drug Delivery Systems: A Review Integrating Pharmaceutics and Regulatory Affairs

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ABSTRACT

Quality by Design (QbD) has evolved from a regulatory aspiration into a foundational scientific framework for the development of novel drug delivery systems (NDDS), including lipid-based nanocarriers, polymeric nanoparticles, self-nanoemulsifying drug delivery systems (SNEDDS), liposomes, and mRNA-lipid nanoparticle (LNP) platforms. Rooted in the International Council for Harmonisation (ICH) Q8-Q12 guideline series, QbD replaces traditional quality-by-testing paradigms with a systematic, risk-based approach built around the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), Design of Experiments (DoE), design space definition, and lifecycle-oriented control strategies. This review integrates the pharmaceutical science underlying QbD implementation in NDDS - including formulation optimization, risk-assessment tools, and process analytical technology (PAT) - with the regulatory affairs perspective governing its application, spanning FDA and EMA expectations, post-approval change management under ICH Q12, and unresolved translational gaps for complex nanopharmaceuticals. Representative case studies across lipid nanosystems, polymeric nanoparticles, and nanoemulsion-based ocular delivery illustrate practical QbD implementation. The review concludes with a discussion of emerging directions, including artificial-intelligence-assisted design-space modelling and analytical QbD (AQbD), and highlights the continuing need for harmonized regulatory frameworks specific to nanopharmaceutical complexity.

Keywords: Quality by Design; ICH Q8-Q12; novel drug delivery systems; nanopharmaceuticals; Design of Experiments; Critical Quality Attributes; regulatory affairs; pharmaceutical development

INTRODUCTION

Pharmaceutical product development has historically relied on a "quality by testing" (QbT) paradigm, in which quality is verified retrospectively through end-product testing against fixed specifications. This reactive approach, while historically effective for conventional oral solid dosage forms, is poorly suited to the structural and functional complexity of NDDS such as liposomes,

polymeric nanoparticles, SNEDDS, and lipid nanoparticle (LNP)-based nucleic-acid carriers, where minor variations in formulation composition or process parameters can substantially alter particle size, encapsulation efficiency, release kinetics, and ultimately clinical performance. Quality by Design represents a paradigm shift: a systematic, scientific and risk-based approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding, based on sound science and quality risk management. Rather than testing quality into a finished product, QbD builds quality into the product and process design from the outset, enabling both improved product robustness and greater regulatory flexibility across the product lifecycle. The framework is formalized through the ICH Q8-Q12 guideline series, harmonized across the FDA, the European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA), providing developers a common scientific and regulatory language worldwide.

NDDS present a particularly compelling application domain for QbD because of their inherent multi-parameter complexity. Nanocarrier attributes such as particle size, polydispersity index, zeta potential, encapsulation efficiency and in vitro release profile are simultaneously influenced by formulation composition (lipid/polymer ratios, surfactant selection, drug loading) and process parameters (homogenization speed, sonication time, mixing rate), making empirical one-factor-at-a-time optimization both inefficient and scientifically insufficient. The present review integrates the pharmaceutics of QbD implementation in NDDS with the regulatory affairs dimension that determines how QbD-derived design spaces and control strategies are evaluated, approved and managed across the product lifecycle, covering (i) core QbD elements and their application to lipid-based nanosystems, polymeric nanoparticles, SNEDDS and mRNA-LNP platforms; (ii) representative case studies; (iii) ICH Q8-Q12 harmonization and post-approval change management; and (iv) unresolved regulatory gaps and future directions for complex nanopharmaceuticals.

MATERIALS & METHODS

This review was compiled through a structured, narrative literature-survey approach rather than an original laboratory investigation. Peer-reviewed articles, systematic and narrative reviews, and primary regulatory guidance documents published principally between 2007 and 2026 were identified through PubMed, ScienceDirect and Google Scholar using combinations of the search terms “Quality by Design”, “QbD”, “novel drug delivery system”, “nanoparticle”, “liposome”, “SNEDDS”, “design space”, “design of experiments” and “ICH Q8-Q12”. Original guideline documents were obtained directly from the ICH, FDA and EMA websites. Articles were selected for inclusion when they described QbD elements (QTPP, CQA, CPP, risk assessment, DoE, design space, control strategy) applied specifically to lipid-based nanosystems, polymeric nanoparticles, SNEDDS or mRNA-LNP platforms, or when they addressed the regulatory affairs dimension of QbD implementation. Ten representative and current sources were selected on this basis for detailed citation, supplemented by direct reference to the primary ICH guidelines; information was synthesized narratively under the pharmaceutics and regulatory-affairs themes summarized above.

RESULTS AND DISCUSSION

QbD Fundamentals and the ICH Regulatory Framework

QbD is formally defined by ICH Q8(R2) 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” (ICH Q8(R2); 2009). Its regulatory foundation rests on five interlinked ICH guidelines, summarized in Table 1.

Table 1. The five harmonized ICH guidelines underpinning the QbD framework.

Guideline	Title	Core Contribution to QbD
ICH Q8(R2)	Pharmaceutical Development	Introduces QTPP, CQAs and design space; establishes the shift from quality-by-testing to quality-by-design.
ICH Q9(R1)	Quality Risk Management	Provides structured risk-assessment tools (FMEA, Ishikawa diagrams, risk ranking) to prioritize CQAs and CPPs.
ICH Q10	Pharmaceutical Quality System	Establishes a lifecycle-based quality system integrating Q8/Q9 outputs into ongoing manufacturing and continual improvement.
ICH Q11	Development and Manufacture of Drug Substances	Extends QbD principles upstream to active pharmaceutical ingredient (API) development and control strategy.
ICH Q12	Technical and Regulatory Considerations for Product Lifecycle Management	Introduces Established Conditions and Post-Approval Change Management Protocols (PACMP) for science-based post-approval change.

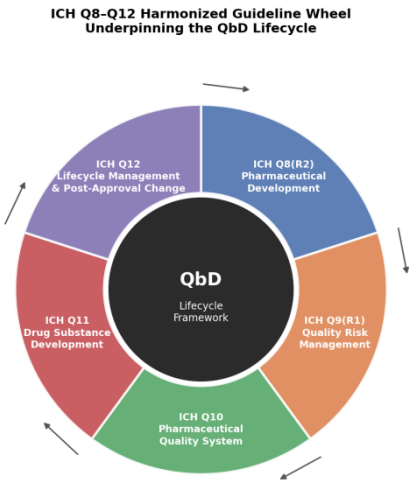

Figure 1. The five harmonized ICH guidelines (Q8-Q12) form an interlinked lifecycle wheel underpinning the QbD framework, from initial pharmaceutical development through post-approval change management.

A central concept introduced by ICH Q8 is the design space, defined as "the multidimensional combination and interaction of input variables (material attributes and process parameters) that have been demonstrated to provide assurance of quality" (ICH Q8(R2); 2009). Regulatory flexibility is explicitly tied to the depth of product and process understanding demonstrated: movement within an approved design space does not require additional regulatory approval, whereas movement outside the design space typically initiates a regulatory change process. This linkage between scientific understanding and regulatory flexibility is a key incentive driving industry adoption of QbD, particularly for complex, multi-parameter NDDS formulations (Gosavi et al.; 2026).

Core Elements of QbD Implementation

Practical implementation of QbD proceeds through a structured, interconnected sequence of elements.

Quality Target Product Profile (QTPP): a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure desired efficacy and safety, considering route of administration, dosage form, bioavailability and stability. For an NDDS such as a nanoemulsion or liposomal formulation, the QTPP typically specifies target particle-size range, drug-release profile, route-specific bioavailability targets and intended shelf-life conditions.

Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs): CQAs are physical, chemical, biological or microbiological properties that must be controlled within an appropriate range to ensure desired product quality. For nanocarrier-based NDDS, common CQAs include particle size and polydispersity index, zeta potential, encapsulation efficiency, drug loading and in vitro release rate. CPPs are the process inputs - such as homogenization speed, sonication energy, lipid-to-drug ratio, or microfluidic flow-rate ratio - whose variability has a direct, demonstrable impact on CQAs.

Quality Risk Management: formalized under ICH Q9(R1), this provides structured tools - FMEA, Ishikawa (fishbone) diagrams, and risk-ranking/filtering - to identify and prioritize which material attributes and process parameters most affect CQAs, focusing experimental work on the variables of greatest consequence.

Design of Experiments (DoE) and Design Space: DoE constitutes the core statistical methodology through which QbD is operationalized in NDDS formulation. Rather than varying one factor at a time, DoE approaches - including full and fractional factorial designs, Box-Behnken designs, central composite designs, Plackett-Burman screening designs and Taguchi designs - allow simultaneous evaluation of multiple factors and their interactions, generating a statistically robust design space with a minimal number of experimental runs. Response-surface methodology is then applied to model relationships between formulation/process variables and CQAs, often supplemented by optimization tools such as overlay plots or artificial neural networks (Panwar et al.; 2026).

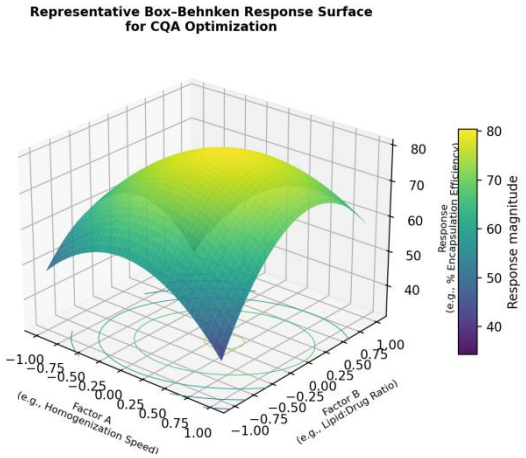

Figure 2. Representative Box-Behnken response surface illustrating how two formulation/process factors (e.g., homogenization speed and lipid-to-drug ratio) jointly influence a critical quality attribute such as percentage encapsulation efficiency.

Control Strategy: informed by the design space and risk assessment, the control strategy defines the planned set of controls that assures process performance and product quality. For NDDS this frequently incorporates in-process controls (e.g., in-line particle-size monitoring), PAT tools, and real-time release testing (RTRT) that reduce reliance on end-product testing alone (Kamankar et al.; 2026).

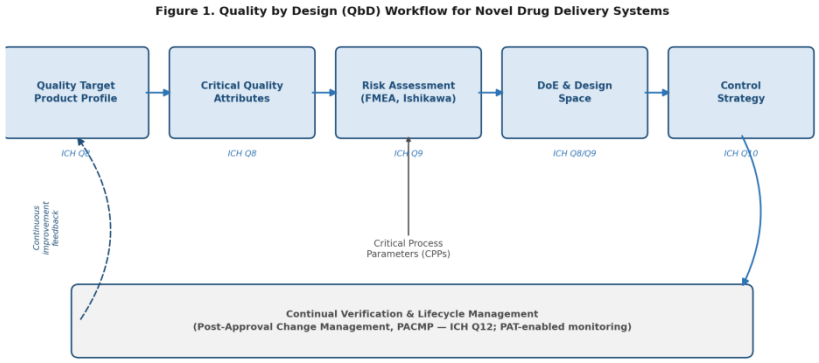

Figure 3. Sequential QbD workflow linking QTPP definition, CQA/CPP identification, risk assessment, DoE-based design-space establishment, and control strategy to lifecycle-oriented post-approval change management under ICH Q8-Q12.

Application of QbD to Novel Drug Delivery Systems

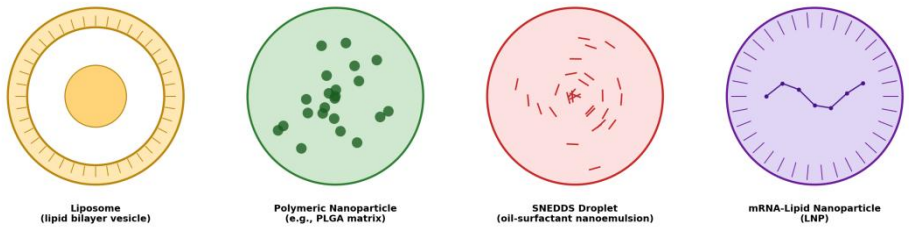

Figure 4. Schematic cross-sections of the major NDDS platforms discussed in this review: the lipid bilayer vesicle of a liposome, a polymeric (e.g., PLGA) nanoparticle matrix, an oil-surfactant SNEDDS nanoemulsion droplet, and an ionizable-lipid mRNA-LNP construct.

Lipid-based nanosystems and liposomes. Regulatory agencies increasingly expect sophisticated analytical characterization and demonstrated correlation between CQAs and in vivo performance for complex products, consistent with the EMA's Regulatory Science to 2025 reflection and corresponding FDA initiatives. For nanoliposomal formulations, QbD-guided development has been applied to diabetes, cardiovascular disease, rheumatoid arthritis and CNS indications, employing factorial, Plackett-Burman, Box-Behnken and Taguchi DoE models alongside neural-network and overlay-plot-based optimization (Atre and Rizvi; 2024).

Polymeric nanoparticles. QbD has been extensively applied to PLGA (poly (lactic-co-glycolic acid)) nanoparticles as a formal optimization tool linking formulation variables (polymer molecular weight, surfactant concentration, organic-to-aqueous phase ratio) to CQAs such as particle size, encapsulation efficiency and drug release (Struzek and Scherließ; 2023), with similar approaches applied to nanoparticulate investigational medicinal products, reflecting growing regulatory acceptance of QbD-derived dossiers.

SNEDDS. Self-nanoemulsifying drug delivery systems, widely used for oral delivery of poorly water-soluble drugs, depend critically on optimized component composition (oil, surfactant, co-surfactant ratios) guided by a predefined QTPP. A representative case study applied Box-Behnken design within a QbD framework to optimize an ocular SNEDDS for flurbiprofen, mapping formulation composition against nanoemulsion CQAs (Jeong et al.; 2025).

Targeted nanoparticle systems. More broadly, QbD-guided formulation and process optimization spanning risk assessment, DoE-based screening and control-strategy development confirm that QbD implementation for nanopharmaceuticals requires an integrated approach across material attributes, process parameters and analytical control (Kamankar et al.; 2026).

Regulatory Affairs Perspective

The regulatory affairs dimension of QbD is inseparable from its pharmaceutical implementation: the scientific rigor of a QbD-derived design space directly determines the degree of regulatory flexibility a developer can expect. The FDA embeds QbD expectations within its Q8/Q9/Q10 Questions-and-Answers guidance, clarifying how design space, control strategy and quality-system elements should be described in submissions, including reduced post-approval supplement requirements for movements within an approved design space. The EMA aligns with ICH Q8-Q12 through its Regulatory Science to 2025 reflection, addressing complex products including nanomedicines and calling for standardized analytical and statistical tools for continuous manufacturing. ICH Q8 and its companion guidelines are harmonized across the FDA, EMA and PMDA, giving a shared regulatory language that reduces duplicative review burden for multinational sponsors; both FDA and EMA have also championed process analytical technology (PAT) as a complement to QbD, favouring real-time, in-process monitoring over traditional end-product testing alone.

ICH Q12 extends QbD into the post-approval phase through Established Conditions (legally binding elements of an approved application) and Post-Approval Change Management Protocols (PACMPs), which let sponsors pre-agree testing and reporting requirements for anticipated future changes. This is particularly consequential for NDDS, whose manufacturing processes are frequently refined post-approval (e.g., scale-up from bench microfluidic mixing to GMP-scale continuous manufacturing); a well-defined design space combined with a PACMP can substantially reduce the associated regulatory burden. A related, increasingly emphasized concept is Analytical Quality by Design (AQbD), which extends the QTPP-CQA-risk-assessment-DoE framework to the analytical methods used to characterize NDDS CQAs, ensuring that methods for particle size, encapsulation efficiency or drug release are themselves robust, validated and fit for purpose (Ameen and Pappula; 2023).

Despite this progress, agencies have acknowledged that quality assessment of complex products, including nanomedicines, still needs more standardized analytical techniques and clearer correlation between CQAs and in vivo performance. Dedicated guidance on nanoparticle-specific attributes (e.g., protein-corona formation, batch-to-batch nanostructural variability) remains less mature than for conventional oral solids, frameworks for real-time release testing and continuous manufacturing are still evolving, and inconsistent application of quality risk management across vendors and regions remains an ongoing implementation challenge (Rawal et al.; 2019).

Challenges, Limitations and Future Directions

- Analytical complexity: NDDS formulations often require multiple, non-standardized analytical techniques to characterize CQAs, complicating DoE-based optimization and regulatory review.
- Scale-up and technology transfer: design spaces set at bench scale frequently require re-verification on pilot/commercial scale, particularly for nanoparticle systems sensitive to mixing geometry and shear.
- Resource and expertise intensity: effective QbD implementation requires substantial statistical, engineering and

regulatory expertise, a barrier for smaller developers and academic groups.

- In vitro-in vivo correlation (IVIVC): robust correlation between CQAs and in vivo performance remains challenging for many nanocarriers, limiting the predictive power of QbD-derived design spaces (Vasave et al.; 2025).

Looking ahead, artificial-intelligence and machine-learning tools are increasingly being integrated into pharmaceutical R&D and are expected to enhance DoE-based design-space modelling, accelerate formulation screening and improve predictive CQA-CPP modelling for complex NDDS. Continued formalization of AQbD is expected to improve regulatory acceptance of the analytical methods required for nanopharmaceutical characterization, continued evolution of FDA/EMA regulatory-science initiatives should yield more nanomedicine-specific guidance, and greater PAT-enabled continuous manufacturing is expected, supported by evolving real-time-release-testing frameworks.

CONCLUSION

Quality by Design has matured from a regulatory concept into an essential scientific and translational framework for the development of novel drug delivery systems. Its structured progression - from QTPP definition through risk assessment, DoE-based optimization, design-space establishment and lifecycle-oriented control strategy - provides a systematic pathway for managing the inherent multi-parameter complexity of nanocarrier and lipid-based delivery platforms. Critically, QbD's pharmaceutical and regulatory dimensions are inseparable: the scientific depth of product and process understanding directly determines the regulatory flexibility afforded under ICH Q8-Q12 harmonized guidance. As NDDS platforms continue to diversify - spanning liposomes, polymeric nanoparticles, SNEDDS and mRNA-LNP systems - continued integration of QbD principles, supported by emerging AI-assisted design tools and maturing nanomedicine-specific regulatory frameworks, will remain central to translating novel delivery platforms from bench-scale innovation to approved, reproducible clinical products.

Declaration by Authors

Ethical Approval: Not applicable (literature-based review; no human or animal subjects were involved).

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Conflict of Interest: No conflicts of interest declared.

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