INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Lasmiditan: A Quality by Design (QbD) Approach Integrated with Artificial Intelligence for Formulation Development — A Comprehensive Review

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ARTICLE INFO

Published: 27 May. 2026
Keywords:
Lasmiditan; Quality by Design; QbD; Artificial Intelligence; Machine Learning; Migraine; 5-HT1F receptor; Critical Quality Attributes; Design Space; Nanotechnology
DOI:
10.5281/zenodo.20414552

ABSTRACT

Lasmiditan (REYVOW®, Eli Lilly), the first approved member of the "ditan" class, represents a paradigm shift in acute migraine therapy through selective 5-HT1F receptor agonism devoid of vasoconstriction. Despite its therapeutic promise, lasmiditan's relatively modest oral bioavailability (~40%) and centrally mediated adverse effects present formulation challenges that call for innovative, science-driven development strategies. Quality by Design (QbD) — a systematic, risk-based pharmaceutical development paradigm rooted in ICH Q8–Q11 guidelines — provides a powerful framework to address these challenges by defining Critical Quality Attributes (CQAs), identifying Critical Process Parameters (CPPs), and establishing robust design spaces. The integration of Artificial Intelligence (AI) and Machine Learning (ML) tools into the QbD framework — now referred to as Quality by Digital Design (QbDD) — further enhances predictive formulation optimization, real-time process control, and regulatory compliance. This review comprehensively discusses lasmiditan's pharmacology, pharmacokinetics, and formulation landscape, then explores how QbD tools — including Ishikawa risk assessment, Design of Experiments (DoE), Response Surface Methodology (RSM), Analytical Quality by Design (AQbD), and AI/ML-driven optimization — can synergistically guide the development of superior lasmiditan drug products, from conventional tablets to nanosystems and alternative delivery routes.

INTRODUCTION

Migraine is a debilitating neurological disorder affecting approximately 1 billion people worldwide and is recognized as one of the leading causes of disability. Despite decades of pharmacological advances, a significant proportion of migraine sufferers remain

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

inadequately treated, either due to lack of efficacy with available agents or contraindications stemming from their cardiovascular risk profiles. Triptans — 5-HT1B/1D receptor agonists — have historically constituted the cornerstone of acute migraine treatment; however, their vasoconstrictive mechanism restricts their use in patients with ischemic heart disease, uncontrolled hypertension, and cerebrovascular disorders. The development of the ditan class of molecules emerged from the recognition that migraine pathophysiology is primarily neuronal rather than vascular. Lasmiditan (formerly COL-144, LY573144), a first-in-class selective 5-HT1F receptor agonist, was approved by the United States Food and Drug Administration (US-FDA) in October 2019 under the brand name REYVOW® for the acute treatment of migraine with or without aura in adults. Unlike triptans, lasmiditan exerts its therapeutic effect exclusively through neuronal pathways, thereby avoiding the vascular adverse events that limit triptan use. Despite this therapeutic advance, lasmiditan's formulation presents notable challenges. Its oral bioavailability is approximately 40%, it has a plasma protein binding of approximately 55–60%, and it crosses the blood–brain barrier — contributing to centrally mediated adverse effects such as dizziness, somnolence, and paresthesia. These characteristics present opportunities for formulation scientists to employ rational, quality-driven strategies to optimize delivery and minimize adverse events. Quality by Design (QbD), as articulated in ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality Systems), and Q11 (Development and Manufacture of Drug Substances), offers a systematic, proactive approach to pharmaceutical development. Rather than relying on end-product testing alone, QbD begins with predefined objectives — the Quality Target Product Profile (QTPP) — and builds product and process understanding through science, risk assessment, and statistical design tools. The incorporation of AI and ML technologies into this framework — enabling predictive modeling, pattern recognition, real-time analytics, and digital twin simulations — constitutes the emerging field of Quality by Digital Design (QbDD), which holds transformative potential for pharmaceutical product development. This review integrates the clinical, pharmacological, and physicochemical context of lasmiditan with a thorough examination of QbD and AI-integrated approaches applicable to its formulation development, analytical method development, and quality assurance.

Lasmiditan: Overview And Pharmacology

Chemical Identity and Structural Features

Lasmiditan (chemical name: 2,4,6-trifluoro-N-(6-(1-methylpiperidine-4-carbonyl)pyridin-2-yl)benzamide; molecular formula: $C_{19}H_{18}F_3N_3O_2$; molecular weight: 393.36 g/mol) belongs structurally to the pyridinoyl-piperidine class. Unlike triptans, which contain an indole core, lasmiditan's absence of the indole moiety contributes to its high selectivity for the 5-HT1F receptor over other serotonergic subtypes. In 2020, lasmiditan became the first ditan to receive US-FDA approval, marking a new chapter in migraine pharmacotherapy.

Mechanism of Action

Lasmiditan is a highly selective agonist of the 5-hydroxytryptamine 1F (5-HT1F) receptor, with a Ki of 2.21 nM and a greater than 470-fold selectivity for the 5-HT1F receptor over the 5-HT1B/D receptors. The 5-HT1F receptor is expressed on terminals and cell bodies of trigeminal ganglion neurons and plays a modulatory role in nociceptive transmission.

Mechanistically, lasmiditan activates 5-HT1F receptors on presynaptic trigeminal nerve terminals, which impedes the release of calcitonin gene-related peptide (CGRP) from trigeminal nerve endings, thereby suppressing activation of the trigeminovascular system. Importantly, unlike triptans that bind 5-HT1B/1D receptors causing direct vascular vasoconstriction, lasmiditan's mechanism of action is exclusively neuronal with no evidence of vasoactive effects. This distinction permits its use in patients with cardiovascular risk factors who are not candidates for triptans. Furthermore, lasmiditan is a highly lipophilic compound that crosses the blood–brain barrier (BBB), allowing it to act both centrally and peripherally on 5-HT1F receptors expressed on the trigeminovascular system. The central mechanism is believed to contribute to its efficacy in central sensitization states, while also accounting for the CNS-related adverse effects observed in clinical trials.

Pharmacokinetics

Lasmiditan demonstrates the following pharmacokinetic profile based on FDA-approved prescribing information and clinical pharmacology studies:

- **Absorption:** Lasmiditan is well absorbed orally. Peak plasma concentration (Tmax) is reached approximately 1.8 hours after oral administration. Oral bioavailability is approximately 40% in humans, attributed in part to first-pass metabolism.
- **Distribution:** Plasma protein binding is approximately 55–60% and is independent of concentration in the range of 15–500 ng/mL. Lasmiditan is highly lipophilic and readily crosses the BBB.
- **Metabolism:** Lasmiditan undergoes hepatic and extrahepatic metabolism primarily by non-CYP enzymes, yielding pharmacologically inactive metabolites. The primary urinary metabolite is S-M8. Because metabolism does not significantly involve cytochrome P450 enzymes, CYP inhibitors or inducers are unlikely to affect lasmiditan pharmacokinetics.
- **Elimination:** The plasma half-life (t1/2) is approximately 5.7 hours, primarily via metabolic elimination with minimal unchanged renal excretion.
- **Food effects:** A high-fat meal slightly increases lasmiditan exposure; however, this is not considered clinically significant.
- **Special populations:** Age, sex, race/ethnicity, and body weight do not significantly affect lasmiditan pharmacokinetics. No dose adjustment is required for mild or moderate hepatic impairment.

Clinical Efficacy

The efficacy of lasmiditan in the acute treatment of migraine was demonstrated in two pivotal, randomized, double-blind, placebo-controlled clinical trials (Study 1: NCT02439320; Study 2: NCT02605174). These studies enrolled adults with a history of migraine with and without aura. For all dose levels examined (50, 100, and 200 mg), lasmiditan demonstrated statistically significant superiority over placebo for the primary endpoint — pain freedom at 2 hours post-dose — and the key secondary endpoint — freedom from the most bothersome symptom at 2 hours. Lasmiditan tablets in doses of 50–400 mg show significant headache relief at 2 hours compared with placebo and improved

accompanying migraine symptoms. The approved doses are 50 mg and 100 mg, with a maximum of one dose per 24 hours. Lasmiditan is classified as a Schedule V controlled substance in the United States due to potential CNS side effects.

Safety Profile

The most common adverse events observed with lasmiditan are CNS-mediated, reflecting the drug's ability to cross the BBB. These include dizziness (15–17%), somnolence (7–9%), paresthesia (5–7%), sedation, and fatigue. Importantly, lasmiditan does not result in vasoconstriction, making it suitable for patients with cardiovascular risk factors who cannot use triptans. Dizziness is more frequent in patients aged ≥65 years (19% vs. 14% in younger patients). Due to CNS effects, patients are advised not to drive or operate machinery for at least 8 hours after taking lasmiditan.

Pharmaceutical Formulation Challenges and Opportunities

The formulation of lasmiditan as an immediate-release oral tablet (REYVOW®) represents the approved commercial approach; however, several formulation challenges and novel opportunities exist:

Bioavailability limitations: The approximately 40% oral bioavailability of lasmiditan leaves room for formulation-driven enhancement, particularly through nanotechnological approaches such as nanosuspensions, nanoemulsions, solid lipid nanoparticles (SLNs), or self-nanoemulsifying drug delivery systems (SNEDDS).

CNS adverse effects: The centrally mediated side effects arise partly from lasmiditan's high lipophilicity and BBB penetration. Formulation strategies that modulate the pharmacokinetic profile — particularly Cmax and the rate of CNS penetration — could potentially reduce side effect burden.

Alternative delivery routes: Intranasal delivery represents a promising route that bypasses first-pass metabolism, potentially improving bioavailability and enabling rapid onset of action relevant to acute migraine management. Studies on nanoemulsion-based in situ gels for intranasal lasmiditan delivery have demonstrated the feasibility and pharmacokinetic advantages of this approach.

Analytical method development: The lack of environmentally sustainable and QbD-guided analytical methods for lasmiditan quantification in bulk and formulations has been identified as a gap, with recent work addressing this through green UV spectrophotometric approaches guided by central composite design.

Quality by Design (QbD): Foundational Framework

Principles and Evolution

QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes understanding product and process, based on sound science and quality risk management. Rooted in ICH Q8–Q11 guidelines, QbD transitions the paradigm from reactive quality testing to proactive, science-driven methodologies, emphasizing the definition of Critical Quality Attributes (CQAs), establishment of design spaces, and integration of risk management to enhance product robustness and regulatory flexibility.

The foundational elements of the QbD framework include:

1. **Quality Target Product Profile (QTPP):** A prospective summary of the desired quality characteristics of the drug product relevant to safety and efficacy.

2. **Critical Quality Attributes (CQAs):** Physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit or distribution to ensure the desired product quality.

3. **Risk Assessment:** Systematic use of available information to identify hazards and estimate risk, typically employing tools such as Ishikawa (fishbone) diagrams, Failure Mode and Effect Analysis (FMEA), and risk ranking.

4. **Design of Experiments (DoE):** Statistical methodologies including factorial designs, Box-Behnken designs, and central composite designs used to systematically evaluate the effects of formulation variables on CQAs.

5. **Design Space:** The multidimensional combination and interaction of input variables (material attributes and process parameters) that have been demonstrated to provide assurance of quality.

6. **Control Strategy:** A planned set of controls, derived from current product and process understanding.

7. **Continual Improvement:** Ongoing monitoring and refinement based on manufacturing experience.

QBD IN FORMULATION DEVELOPMENT

QbD has been successfully applied across a broad spectrum of pharmaceutical dosage forms — oral tablets, injectables, nanotechnology-based systems, modified-release formulations, and biologics. A critical recognition from the QbD framework is that quality cannot be adequately tested into products but must be built in during design. Traditional quality-by-testing (QbT) approaches, rooted in end-product testing and reactive quality control, often foster siloed workflows and a checklist mentality. In contrast, QbD emphasizes a proactive approach where CQAs and CPPs are identified and controlled during the development process. This not only mitigates risks but also facilitates continuous improvement and adaptability in manufacturing processes.

Analytical Quality by Design (AQbD)

Analytical Quality by Design (AQbD) applies QbD principles specifically to the development, validation, and routine use of analytical methods. The framework involves defining the Analytical Target Profile (ATP), identifying Method Operable Design Regions (MODR), and optimizing method parameters through systematic DoE approaches. AQbD ensures that analytical methods are robust, validated per ICH Q2(R1) guidelines, and suitable for their intended purpose throughout the product lifecycle.

QbD-Guided Formulation and Analytical Development of Lasmiditan

Defining the QTPP and CQAs for Lasmiditan Formulations

For a lasmiditan immediate-release oral tablet (or novel formulation), a representative QTPP would specify the intended use (acute migraine treatment in adults), route of administration (oral), dosage form (tablet or novel nanoformulation), dosage strength (50 mg or 100 mg), and desired pharmacokinetic profile (rapid absorption, Tmax ~1.8 h). CQAs would include drug content and

uniformity, dissolution profile, disintegration time, particle size and size distribution (for nanoformulations), zeta potential, assay and related substances, moisture content, and hardness/friability. For nanotechnology-based lasmiditan formulations, additional CQAs would include particle size (target: <200 nm for enhanced bioavailability), polydispersity index (PDI; target: <0.3 for homogeneity), zeta potential (target: ≥±20 mV for physical stability), encapsulation efficiency (target: >80%), and drug release profile.

Risk Assessment

Risk assessment using Ishikawa diagrams would identify critical input variables affecting lasmiditan formulation CQAs: raw material attributes (drug particle size, polymorphic form, solubility), excipient properties (type and concentration of surfactants, co-surfactants, polymers), and process parameters (mixing speed and duration, emulsification temperature, homogenization pressure, drying parameters). FMEA scoring enables prioritization of which variables require systematic investigation through DoE.

Design of Experiments and Response Surface Methodology

Following risk assessment, high-risk variables are investigated using appropriate DoE designs. For lasmiditan nanoemulsions or SNEDDS, central composite design (CCD) or Box-Behnken design (BBD) may be applied to study the effects of variables such as oil phase type and concentration, surfactant:co-surfactant ratio (Smix), and drug loading on CQAs including droplet size, PDI, zeta potential, and drug release. Response Surface Methodology (RSM) generates polynomial mathematical models relating input variables to responses, enabling optimization within the design space.

A recent study developing a QbD-guided green UV spectrophotometric method for lasmiditan quantification employed Central Composite Design (CCD) to optimize method parameters, achieving excellent linearity over 2–22 µg/mL (R^2 = 0.999) and robustness as validated per ICH guidelines. The method was applicable to both bulk drug and nanosuspension analysis, and greenness assessment confirmed minimal environmental impact.

Nanotechnology-Based Approaches and QbD

Recent research has explored intranasal nanoemulsion-based in situ gel (NEIG) formulations for lasmiditan to improve bioavailability via nasal delivery. In these studies, nanoemulsions incorporating different oil phases, emulsifiers, and co-emulsifiers were systematically optimized, with Carbopol 934 added as a pH-sensitive in situ gelling polymer. In situ gelation at nasal pH provides prolonged mucosal contact time, enhanced permeation, and improved relative bioavailability compared to aqueous lasmiditan suspension. The QbD framework would systematically define the QTPP for such intranasal systems, identify CQAs (droplet size, viscosity, drug permeation flux), perform risk assessment, and optimize through DoE. Similarly, QbD-driven development of lasmiditan nanosuspensions, SLNs, SNEDDS, and polymeric nanoparticles would follow the systematic workflow: QTPP → CQA identification → risk assessment → DoE → design space establishment → control strategy → validation.

RP-HPLC and AQbD for Lasmiditan

Stability-indicating RP-HPLC methods for lasmiditan quantification in tablet dosage forms have been developed and validated according to ICH Q2(R1) guidelines for accuracy, precision,

linearity, specificity, robustness, and sensitivity. LC-MS/MS methods have also been developed with excellent sensitivity (LOD: 0.66 ng/mL; LOQ: 2.22 ng/mL), using Acetonitrile: 0.1% formic acid (70:30) mobile phase on a C18 column, with [M+H]+ ion m/z ratio of 378.24 monitored in positive ion mode by MRM. Applying AQbD to these analytical methods would systematically identify the Analytical Target Profile, screen critical analytical factors (CAFs) via Plackett-Burman or fractional factorial designs, optimize using CCD or BBD, and establish the Method Operable Design Region.

Artificial Intelligence Integration with QbD in Lasmiditan Development

The Convergence of AI and QbD

The integration of AI and ML into the QbD framework has been described as Quality by Digital Design (QbDD) — a significant advancement in pharmaceutical quality management that combines scientific principles with advanced digital technologies to optimize drug development and manufacturing. Traditional QbD approaches relying on physical experimentation and classical statistical modeling are enhanced by AI tools that provide predictive capabilities, handle complex multivariate data, and enable continuous process verification. Recent advances in AI and ML are revolutionizing nanopharmaceutical development by enabling data-driven formulation design, process optimization, and real-time quality prediction. Machine learning and deep learning models have been employed to predict critical quality attributes from CPPs, while natural language processing (NLP) has been applied to manage regulatory documentation. Explainable AI (XAI) techniques, including SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-agnostic Explanations), ensure interpretability and compliance with ICH Q8–Q11 guidelines.

Machine Learning for Formulation Optimization

Several ML architectures hold particular promise for QbD-driven lasmiditan formulation development:

Artificial Neural Networks (ANNs): ANNs can model complex, non-linear relationships between formulation variables (input neurons) and CQAs (output neurons), enabling predictive formulation optimization beyond the capabilities of classical polynomial response surface models. ANNs applied to quality-by-design frameworks have been reported to predict dissolution profiles, particle size, and drug release from input formulation parameters.

Gaussian Process Regression (GPR) / Bayesian Optimization: These approaches are well-suited to pharmaceutical DoE scenarios with limited experimental data points, enabling efficient exploration of design spaces and uncertainty quantification.

Random Forest and Gradient Boosting: Ensemble learning methods can identify the most important formulation and process variables contributing to CQA variability (feature importance), complementing traditional Pareto analysis in QbD.

Deep Learning: Convolutional neural networks and recurrent neural networks can analyze complex manufacturing process data streams (from PAT tools such as NIR, Raman, and particle size analyzers) in real time, enabling process control and early fault detection.

Digital Twins in QbD

Digital twins — virtual, real-time computational replicas of a pharmaceutical manufacturing process — represent a frontier application of AI in QbD. By integrating mechanistic models (process analytical technology data, first-principles equations) with data-driven ML models, digital twins can simulate process behavior under various conditions, predict deviations before they occur, and support real-time release testing (RTRT) without requiring physical batch testing. The combination of AI, digital twins, and QbD constitutes the Pharma 4.0 vision for intelligent, adaptive manufacturing.

Natural Language Processing and Regulatory Intelligence

AI-driven NLP tools can parse extensive regulatory documents — FDA guidance, ICH guidelines, EMA assessment reports — and automatically extract relevant provisions for QbD submissions. This accelerates the compilation of regulatory dossiers, assists in gap analysis, and ensures alignment of the development strategy with current regulatory expectations.

AI for Predictive Pharmacokinetic Modeling

In the context of lasmiditan, AI models trained on physicochemical descriptors (lipophilicity, pKa, molecular weight, polar surface area) and formulation parameters can predict the pharmacokinetic impact of formulation changes — for example, the effect of particle size reduction on Cmax, Tmax, and AUC, or the influence of nasal absorption on brain penetration dynamics. Population pharmacokinetic (PopPK) models enriched by machine learning inputs can further guide optimal dose and formulation selection.

Specific AI Applications in Lasmiditan QbD

For lasmiditan specifically, the following AI-QbD integration points are envisioned:

- **Solubility and dissolution prediction:** QSAR-based ML models predicting aqueous solubility of lasmiditan under different pH conditions, guiding selection of solubilizing excipients and formulation pH.
- **Nanoformulation optimization:** ANN or Gaussian process models relating oil, surfactant, and co-surfactant compositions to nanoemulsion droplet size and drug release, replacing exhaustive experimental screening.
- **Stability prediction:** ML models trained on lasmiditan degradation data (forced degradation studies) to predict shelf-life under various storage conditions, accelerating ICH stability studies.
- **Analytical method optimization:** AQbD combined with ML for simultaneous optimization of multiple analytical parameters (wavelength, mobile phase composition, pH, column temperature) in HPLC method development.
- **Real-time process monitoring:** PAT-integrated deep learning models for monitoring tablet compression (hardness, weight uniformity) or nanoparticle formation (size, PDI) in real time during manufacturing.

Regulatory Perspectives on QbD and AI

ICH Guidelines

The QbD framework is underpinned by a suite of ICH guidelines: ICH Q8(R2) — Pharmaceutical Development; ICH Q9(R1) — Quality Risk Management; ICH Q10 — Pharmaceutical Quality

System; ICH Q11 — Development and Manufacture of Drug Substances; and ICH Q14 — Analytical Procedure Development. Together, these guidelines provide harmonized international expectations for science- and risk-based pharmaceutical development, supporting regulatory flexibility and enabling post-approval changes within the established design space.

FDA and EMA Expectations

Both the US-FDA and EMA have issued guidance endorsing the QbD paradigm for pharmaceutical development. FDA's Process Analytical Technology (PAT) guidance and the Q8(R2) guideline encourage manufacturers to define design spaces and implement control strategies that assure product quality. EMA's European Medicines Agency assessment reports for drugs such as lasmiditan (RAYVOW® in Europe) evaluate the comprehensive non-clinical and clinical programs, pharmacokinetic analyses, and quality dossiers in line with QbD expectations.

AI in Regulatory Submissions

Regulatory agencies are increasingly acknowledging AI and ML as valid tools in pharmaceutical development and quality assurance. The FDA has issued discussion papers on AI/ML in drug manufacturing, emphasizing the need for model transparency, validation, and interpretability — requirements addressed by XAI tools. Integration of AI-generated predictions and models into QbD regulatory submissions, with appropriate validation and uncertainty quantification, is expected to become standard practice in the coming years.

Challenges And Future Directions

Despite the well-recognized benefits of QbD, its implementation faces several challenges. A significant knowledge gap exists in formal training in QbD tools such as risk assessment matrices and DoE, with many quality assurance personnel lacking proficiency in these methods. Organizational resistance to changing established workflows, the cost of implementing digital QbD infrastructure, and the complexity of validating AI/ML models for regulatory submissions are additional barriers. For lasmiditan specifically, the absence of QbD-guided nanotechnology-based formulation studies is a gap in the literature. The development of more targeted delivery systems — such as CNS-targeted nanoparticles that could selectively deliver lasmiditan to trigeminal ganglia while minimizing systemic CNS penetration and associated adverse effects — represents an exciting but technically challenging frontier.

FUTURE PERSPECTIVES

Future developments in lasmiditan QbD may encompass:

- **Integrated QbD-AI pipelines** for end-to-end formulation development, from in silico screening through process optimization to regulatory submission.
- **Oral modified-release formulations** reducing CNS Cmax while maintaining therapeutic plasma levels, developed using QbD-guided release-retarding technologies.
- **Orally disintegrating tablets (ODTs)** or sublingual formulations providing faster onset during acute migraine attacks, optimized via DoE.
- **Transdermal patches or microneedle systems** bypassing first-pass metabolism and CNS peak exposure, guided by QbD design space concepts.

- **Personalized medicine approaches** using ML-based PopPK models to individualize lasmiditan dosing based on patient-specific genetic, physiological, and co-medication factors.

- **Continuous manufacturing** platforms with embedded PAT and AI-driven process control for lasmiditan tablet manufacturing.

- **Green analytical chemistry integration** within AQbD frameworks, leveraging CCD-optimized green UV and HPLC methods to align with sustainability goals.

CONCLUSION

Lasmiditan represents a landmark in acute migraine therapy, offering a neurally selective, cardiovascular-safe alternative to triptans through its unique 5-HT1F receptor agonism. Its pharmacological and physicochemical profile creates both formulation challenges — particularly around bioavailability enhancement, reduction of CNS adverse effects, and alternative delivery route exploration — and rich opportunities for the application of QbD principles. The QbD framework, grounded in ICH Q8–Q11 guidelines, provides the scientific infrastructure to systematically define product quality targets, assess risks, and optimize formulation and manufacturing through DoE, response surface methodology, and design space establishment. The integration of AI and ML tools — embodied in the QbDD concept — amplifies QbD's power by enabling predictive optimization, real-time process analytics, digital twin simulations, and NLP-driven regulatory intelligence. Together, these approaches can drive the development of next-generation lasmiditan formulations that are safer, more efficacious, and manufactured with greater consistency.

As the pharmaceutical industry progresses toward Pharma 4.0, the synergistic application of QbD and AI to drugs like lasmiditan will serve as a model for intelligent, patient-centric, and regulatorily compliant drug development. Continued investment in interdisciplinary training, digital infrastructure, and validated AI models will be essential to fully realize this potential.

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HOW TO CITE: Abdulla Yazeed, Praseetha. K.*, Lasmiditan: A Quality by Design (QbD) Approach Integrated with Artificial Intelligence for Formulation Development — A Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 7427-7438. https://doi.org/10.5281/zenodo.20414552