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Review Paper

Integration of Quality by Design (QbD) with green chemistry in pharmaceutical Analysis: A sustainable Approach

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ABSTRACT

The pharmaceutical industry faces a dual obligation: ensuring the unimpeachable quality of drug products while simultaneously curtailing the environmental burden of their analysis and manufacture. Quality by Design and green chemistry are two paradigms which, when integrated, offer a coherent and scientifically rigorous framework to achieve both objectives concurrently. QbD, formalised through international council for Harmonisation (ICH) guidelines Q8(R2), Q9(R1), Q10, Q14, and Q2(R2), mandates a systematic, risk based approach to analytical method development centred on the analytical target profile (ATP), Critical method parameters (CMP's), and the Method operable design region (MODR), employing tools such as failure mode and effect analysis (FMEA), Ishikawa diagrams, and design of experiment (DoE). Green chemistry, articulated by Anastas and Warner through 12 foundational principles, seeks to eliminate or minimise hazardous substance and energy consumption at the design stage of chemical processes, including analytical procedure. The integration of these frameworks is operationalised through green analytical chemistry metric tools: National Environmental Method Index (NEMI), Analytical Eco scale (AES), Green analytical procedure index (GAPI), and the analytical Greenness metric (AGREE), which provide quantitative sustainability scores that serve as additional response variables in multi-objective DoE optimisation. This review critically evaluates published case studies across high performance liquid chromatography (HPLC), Ultra high-performance liquid chromatography (UPLC), Micellar electrokinetic capillary chromatography, UV visible spectroscopy, near infrared spectroscopy and electro analytical techniques, demonstrating the practical realisation of the integrated approach. Regulatory framework, current limitations and future directions including machine learning assisted DoE, miniaturised platforms, real time release testing (RTRT), and sustainable novel solvents are discussed. A consolidated QbD Green chemistry workflow is proposed as an actionable guide for pharmaceutical analysts and M Pharm students seeking to

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implement this paradigm in practice.

INTRODUCTION

The pharmaceutical industry operates within one of the most rigorously regulated analytical environments in the world. Analytical methods underpin every stage of the drug product lifecycle—from early-stage raw material characterisation through process monitoring, finished product release testing, stability studies, and post-market surveillance. The obligation to assure product quality whilst minimising the environmental and occupational health footprint of analytical operations has grown steadily more pressing, driven by regulatory evolution, institutional sustainability commitments, and the practical economics of large-scale pharmaceutical manufacturing^[1]

Traditional approaches to analytical method development were empirical and univariate: one variable was changed at a time (OFAT), and the resulting method was validated according to ICH Q2(R1) criteria for specificity, linearity, accuracy, precision, detection and quantitation limits, range, and robustness.^[2] Such methods provided limited understanding of variable interactions, method boundaries, or real-world robustness, and generated no systematic pressure toward greener reagent choices or reduced solvent consumption.

QbD emerged as a transformative paradigm with publication of ICH Q8(R2) in 2009, complemented by Q9 (risk management), Q10 (quality systems), and most significantly ICH Q14 (Analytical Procedure Development, 2022)—the first ICH guideline explicitly addressing analytical method development under a QbD approach^[3,4,5] Q14 establishes the Analytical Target Profile (ATP), endorses the MODR concept, and supports submission of enhanced method development data, enabling post-approval within-MODR adjustments without prior regulatory approval—a significant operational incentive for industry

adoption.^[3] Concurrently, Green Analytical Chemistry (GAC) matured from aspirational principles into a toolbox of quantitative metrics^[6] The 12 Principles of Green Chemistry, first articulated by Anastas and Warner in 1998,^[7] were adapted to analytical chemistry by Namiesnik and colleagues, who established the conceptual vocabulary of waste minimisation, direct analysis, and solvent reduction in analytical practice.^[6] The convergence of QbD and Green Chemistry constitutes a practical, operationalizable strategy for developing pharmaceutical analytical methods that are simultaneously scientifically sound, regulatory-compliant, and environmentally responsible. The DoE framework central to QbD enables multi-objective optimisation incorporating green metrics such as AGREE^[8] and AES^[9] as response variables alongside chromatographic resolution and sensitivity, identifying operating conditions that satisfy all goals simultaneously^[10, 11]

This review aims to provide a comprehensive, critical synthesis of the literature on the integration of QbD with Green Chemistry in pharmaceutical analysis. It establishes theoretical foundations of each paradigm independently, examines the tools and metrics through which integration is achieved, surveys case study evidence across diverse drug classes and analytical techniques, and addresses regulatory perspectives, challenges, and future directions.

FOUNDATIONS OF QUALITY BY DESIGN IN PHARMACEUTICAL ANALYSIS

Historical Development and Regulatory Context

The intellectual origins of QbD in pharmaceutical science trace to Joseph M. Juran's quality planning concepts, emphasising the importance of designing quality into products from the outset rather than testing it in post-hoc. The



pharmaceutical adaptation was catalysed by FDA Process Analytical Technology (PAT) initiatives in the early 2000s, which sought to modernise pharmaceutical manufacturing through real-time monitoring and scientific principles.^[12]

The ICH Q8(R2) guideline introduced the Quality Target Product Profile (QTPP) and design space concept, establishing the philosophical template for QbD in pharmaceutical development^[1] The subsequent Q9(R1) and Q10 guidelines provided risk management and quality system frameworks within which QbD operates.^[5] The landmark ICH Q14 guideline, finalised in 2022, explicitly establishes the ATP as the analytical counterpart to the QTPP and endorses the MODR as the analytical equivalent of the pharmaceutical design space^[3]

The ICH Q2(R2) revision (2022), harmonised with Q14, updated the classical validation framework to accommodate QbD-developed methods, including performance characterisation across the MODR rather than at a single operating point^[4] The FDA and EMA have both issued reflection papers supporting QbD approaches and indicating acceptance of enhanced analytical method submissions that define a MODR, enabling post-approval method adjustments without prior regulatory approval^[3,4]

KEY ELEMENTS OF THE QBD FRAMEWORK FOR ANALYTICAL METHODS

Analytical Target Profile (ATP)

The ATP, defined in ICH Q14, is a prospective statement of the performance characteristics an analytical procedure must achieve to be fit for its intended purpose^[3] It encompasses specificity, accuracy, precision (repeatability and intermediate precision), linearity, range, detection and quantitation limits, and robustness criteria, all defined at the outset of method development. The

ATP drives every subsequent development decision, ensuring that method optimisation is goal-directed rather than arbitrary. Sustainability criteria—minimum acceptable AGREE score, maximum permissible organic solvent volume per analysis, maximum waste generation—can and should be incorporated into the ATP when developing an integrated QbD-Green method^[8,10]

Risk Assessment Tools

Risk assessment tools are applied early in the QbD workflow to identify Critical Method Attributes (CMAs) and Critical Method Parameters (CMPs). The Ishikawa (fishbone) diagram provides a visual cause-and-effect mapping of method parameters onto performance attributes^[13] Failure Mode and Effects Analysis (FMEA) assigns risk priority numbers (RPNs) based on the severity, probability, and detectability of potential failure modes^[5,13] Outputs of risk assessment directly inform factor selection for subsequent DoE studies, ensuring experimental effort is focused on parameters with genuine potential to affect method performance.

Design of Experiments (DoE)

DoE represents the most powerful and distinctive tool in the QbD toolkit. Unlike OFAT approaches, DoE examines multiple factors simultaneously in a structured, statistically sound experimental design, enabling estimation of main effects, interaction effects, and curvature effects with a fraction of the experimental effort required by full factorial exploration^[13] Commonly employed designs in pharmaceutical analytical QbD include: Plackett-Burman (PB) designs for screening (identifying significant factors from a large candidate set using $n+1$ experiments for n factors); Box-Behnken Designs (BBD) for response surface modelling without requiring extreme factor combinations; Central Composite Designs (CCD) for full quadratic response surface modelling; and



D-optimal designs for constrained or irregular experimental regions^[13,14] Experimental data from DoE studies are fitted to mathematical response surface models by multivariate regression. Overlay of multiple response surface models—for resolution, peak tailing, analysis time, and green metric score—produces a graphical MODR that simultaneously satisfies all ATP requirements^[10,11]

Method Operable Design Region (MODR)

The MODR is the multidimensional factor space within which method performance is demonstrated to meet all ATP requirements with high statistical confidence. Its definition is the culmination of the QbD development process^[3]. For methods operating within an approved MODR, minor adjustments to method parameters do not require prior regulatory approval, provided adjustments remain within the MODR—a powerful commercial and operational advantage^[3,1] Monte Carlo simulation and interval analysis are used to evaluate MODR robustness and probability of compliance^[15, 16]

Method Validation Within the QbD Framework

Method validation under QbD, as articulated in ICH Q2(R2) and contextualised by Q14, characterises performance across the MODR rather than at a single operating point^[4,3] This is conceptually aligned with the "Accuracy Profile" approach to validation, which provides a probabilistic assessment of the proportion of analytical results expected to fall within predefined acceptance criteria across the design space^[2]. Validation thus provides statistical confidence that the method meets ATP requirements not just under nominal conditions but throughout the claimed MODR.

FOUNDATIONS OF GREEN CHEMISTRY AND GREEN ANALYTICAL CHEMISTRY

The 12 Principles of Green Chemistry

Green Chemistry was formally defined through the 12 Principles articulated by Paul T. Anastas and John C. Warner in their 1998 monograph "Green Chemistry: Theory and Practice."^[7] Their application to analytical chemistry has been the subject of sustained scholarly attention since the early 2000s, culminating in the establishment of Green Analytical Chemistry (GAC) as a recognised sub-discipline^[6]

The 12 Principles most directly applicable to analytical method development are: (1) Prevention—prevent waste rather than treat it; (2) Atom Economy—maximise incorporation of starting materials into products, translating in analysis to minimal sample and reagent volumes; (3) Less Hazardous Synthesis—use and generate substances with little toxicity; (5) Safer Solvents and Auxiliaries—avoid auxiliary substances where possible, and when used make them innocuous; (6) Energy Efficiency—minimise energy requirements; (10) Design for Degradation—breakdown into innocuous degradation products; and (11) Real-time Analysis—enable in-process monitoring to avoid formation of hazardous substances.^[7,6]

Evolution Towards Green Analytical Chemistry (GAC)

The formal articulation of GAC as a discipline is attributed primarily to Janusz Namiesnik and colleagues at Gdansk University of Technology, whose series of review papers from the early 2000s established the conceptual framework and vocabulary of the field.^[6] Namiesnik defined GAC as the development and application of analytical procedures that reduce hazards to human health and environment whilst achieving equivalent or superior analytical performance.

Key GAC strategies applicable to pharmaceutical analysis include: minimisation of sample preparation steps and volumes; replacement of



organic solvents with water-based or less hazardous alternatives; use of direct analysis techniques; miniaturisation of analytical platforms; and use of renewable or recyclable reagents and solvents.^[6] These strategies align closely with the efficiency-maximisation goals of QbD, creating natural synergies the integrated framework exploits.

Green Metric Assessment Tools

A critical enabler of the quantitative integration of green chemistry with QbD has been the development of numerical green metric tools. These assign quantitative scores to analytical procedures based on environmental, health, and safety (EHS) profiles, enabling objective comparison and incorporation as DoE response variables.^[8,9,17]

National Environmental Method Index (NEMI)

NEMI, proposed in 2003, evaluates procedures against four binary criteria: use of persistent, bioaccumulative, or toxic (PBT) chemicals; hazardous chemical use; hazardous waste generation; and extreme pH (below 2 or above 12). Methods satisfying all four criteria are classified as "green."^[17] Whilst NEMI provides a simple, easily communicable result, its binary nature limits discriminatory power and ability to drive incremental improvements.

Analytical Eco-Scale (AES)

The AES, developed by Van Aken, Schepdael, Sinnaeve, and Deconinck in 2011, uses a penalty-point system starting from 100, subtracting points for hazardous reagents, energy consumption, waste generation, and occupational hazards.^[9] Scores above 75 denote "excellent green analysis," 50–75 "acceptable green analysis," and below 50 "inadequate green analysis." The continuous, quantitative AES score is directly amenable to use as a DoE response variable.

Green Analytical Procedure Index (GAPI)

GAPI, developed by Plotka-Wasyłka in 2016, uses a pictographic "traffic light" system based on five pentagons representing: sample collection and storage; sample preparation; analytical technique; reagents and solvents; and waste management.^[18] Each pentagon is subdivided into assessment fields scored green, yellow, or red for low, moderate, or high concern respectively. A revised version published in 2018 added additional assessment criteria covering the full analytical procedure lifecycle.^[17]

Analytical Greenness Metric (AGREE)

AGREE, proposed by Nowak, Kochana, and Pachla-Wisniewska in 2021, represents the most comprehensive and quantitatively rigorous of currently available green metric tools.^[8] It evaluates procedures against all 12 principles of GAC, assigning a numerical score from 0 (least green) to 1 (fully green) with a colour-coded circular pictogram. AGREE weights each principle according to relative importance and provides a single composite score fully comparable across different analytical procedures and techniques, making it optimal for DoE integration.

Blue Applicability Grade Index (BAGI)

BAGI, introduced by Nowak and Plotka-Wasyłka in 2021 as a complement to AGREE, evaluates practical applicability and economic feasibility of analytical procedures.^[15] BAGI considers sample throughput, cost per analysis, instrument availability, and skill requirements, providing a "blue" applicability score. The combination of AGREE and BAGI scores enables comprehensive multi-criteria optimisation within a QbD framework, balancing sustainability with operational practicality.



Table 1: Comparison of Green Metric Assessment Tools Used in Pharmaceutical Analytical QbD

Metric	Year	Score Type	Score Range	Principles Covered	Optimal QbD Role
NEMI	2003	Binary (Pass/Fail)	Pass / Fail	4 binary criteria	Rapid preliminary screening
Analytical Eco-Scale (AES)	2011	Penalty-point	0–100	Reagents, waste, energy, hazards	DoE response; method comparison
GAPI	2016/2018	Pictographic (G/Y/R)	Colour fields	Full analytical lifecycle	Visual EHS communication
AGREE	2021	Composite numerical	0–1	All 12 GAC principles	Primary DoE response for optimisation
BAGI	2021	Applicability score	0–100	Practicality, cost, throughput	Multi-criteria optimisation with AGREE

INTEGRATION OF QbD AND GREEN CHEMISTRY: A UNIFIED FRAMEWORK

Conceptual Basis for Integration

The conceptual alignment between QbD and Green Chemistry arises from their shared emphasis on proactive, knowledge-led design rather than reactive empirical trial-and-error^[1,7] Both paradigms reject the notion that quality can be assured purely through post-hoc testing, and both mandate systematic exploration of design space to identify optimal operating conditions satisfying multiple performance criteria simultaneously.

In practical terms, integration is achieved by incorporating green metric scores—AGREE,^[8] AES,^[9] or GAPI^[10,11] Conventionally, QbD method optimisation considers responses such as chromatographic resolution (Rs), peak symmetry (As), retention time, and sensitivity. The QbD-Green integration adds AGREE score, AES penalty points, organic solvent consumption volume, waste generation, and energy consumption as additional simultaneous optimisation targets. Desirability function analysis

converts all responses to a common 0–1 scale and computes a composite desirability that is maximised to identify the globally optimal operating point.^[14,13]

Systematic Workflow for Integrated QbD-Green Analytical Method Development

A systematic workflow for integrated QbD-Green Chemistry method development, synthesised from current literature and regulatory guidance, proceeds through six stages:^[3,4,10,13]

- Stage 1 – ATP Definition: Establish required performance criteria including specificity, precision, accuracy, and linearity. Explicitly include sustainability criteria in the ATP: minimum acceptable AGREE score, maximum permissible organic solvent consumption per analysis, and acceptable waste generation limits.^[3,8]
- Stage 2 – CMP Identification and Screening: Generate candidate method parameters via literature review and expert consultation. Apply FMEA and Ishikawa diagrams to prioritise parameters. Apply a Plackett-Burman or fractional factorial screening DoE



to identify parameters with significant effects on both analytical performance and green metrics.^[13,5]

- Stage 3 – Response Surface Optimisation: Apply BBD or CCD to systematically explore critical parameters across all analytical performance and green sustainability responses. Fit polynomial models and validate via ANOVA, R^2 , lack-of-fit test, and residual analysis.^[14,13]
- Stage 4 – MODR Construction: Use overlay contour plots and desirability function optimisation to define the MODR satisfying all analytical performance and sustainability targets simultaneously. Evaluate MODR robustness with Monte Carlo simulation.^[3,11]
- Stage 5 – Validation of the Optimised Green Method: Validate per ICH Q2(R2) and Q14 at the optimal point and MODR boundaries. Calculate and document AGREE, AES, GAPI, and BAGI scores. Compare against benchmark methods to quantify sustainability improvements.^[4,3,8,15]
- Stage 6 – Documentation and Regulatory Submission: Prepare documentation including ATP, risk assessment outputs, DoE plan and results, response surface models, MODR definition, and green metric scores. Submit under the enhanced approach supported by ICH Q14.^[3]

Selection of Experimental Designs for Integrated Optimisation

The choice of experimental design within the integrated QbD-Green framework is governed by the number of critical factors, the degree of model complexity required, practical experimental constraints, and the nature of the response surface.^[13,14] For complex multi-response optimisation incorporating green metrics, CCD and BBD are preferred due to their ability to fit second-order response surface models capturing

the curvature of responses such as chromatographic resolution and AGREE score in the vicinity of the optimum.^[14]

Mixture designs are particularly relevant to green mobile phase optimisation, where mobile phase component fractions must sum to unity, creating a constrained experimental region requiring dedicated design strategies.^[19] Simplex-lattice and simplex-centroid designs enable simultaneous optimisation of mobile phase composition across ternary or quaternary solvent mixtures whilst incorporating green metric evaluation of alternative solvent systems.

APPLICATIONS IN PHARMACEUTICAL ANALYSIS: CASE STUDIES AND EVIDENCE

High-Performance Liquid Chromatography (HPLC)

HPLC remains the most widely employed technique in pharmaceutical analysis, and consequently the largest body of literature on QbD-Green Chemistry integration pertains to HPLC method development.^[14,20] The critical role of mobile phase composition and flow rate in determining both chromatographic performance and solvent consumption makes HPLC particularly amenable to multi-objective QbD-Green optimisation.

Orlandini et al. published landmark studies demonstrating simultaneous optimisation of analytical performance and greenness in HPLC methods for pharmaceutical compounds. Employing Box-Behnken designs with acetonitrile/methanol/buffer mobile phase variables and column temperature as factors, these authors incorporated AES penalty points alongside chromatographic responses in desirability function optimisation.^[10,11] The approach reduced acetonitrile consumption substantially compared



to reference pharmacopoeial methods whilst maintaining complete baseline resolution of all analytes, establishing a methodological template widely adopted in subsequent literature.

Kumar et al. applied a QbD framework with Plackett-Burman screening followed by Box-Behnken optimisation to develop a green RP-HPLC method for simultaneous estimation of amlodipine and Olmesartan in combined antihypertensive tablets.^[21] Risk assessment using an Ishikawa diagram identified mobile phase acetonitrile content, buffer concentration, and pH as critical method parameters. DoE optimisation achieved an AES score of 76 (excellent green) at the optimal operating point, with robustness demonstrated across the established MODR.

Chavez-Blanco et al. demonstrated DoE-optimised HPLC methods for simultaneous determination of metformin and glipizide in combined antidiabetic formulations.^[22] A central composite design optimised mobile phase pH, organic modifier fraction, and flow rate, with AES and analysis time as co-optimised responses. The resulting method employed an ammonium formate/methanol mobile phase, replacing a conventional acetonitrile-phosphate buffer system, achieving a 40% reduction in organic solvent use alongside a 25% reduction in analysis time without compromise of analytical performance.

Sahu et al. provided comprehensive methodological guidance on the application of experimental designs in HPLC method development and validation within pharmaceutical QbD frameworks, documenting design selection criteria, model validation approaches, and MODR construction strategies across multiple drug classes.^[14]

Ultra-Performance Liquid Chromatography (UPLC)

UPLC, employing sub-2- μm particle columns at higher operating pressures, inherently offers significant greenness advantages through dramatically reduced analysis times and mobile phase volumes. Integration of QbD with UPLC development amplifies these advantages by enabling systematic identification of operating conditions that maximise these efficiencies.^[23]

Patel et al. demonstrated QbD-based development of a UPLC method for the simultaneous determination of multiple antihypertensive drugs.^[23] A central composite design was used to optimise gradient conditions, flow rate, and column temperature. The final method consumed substantially less mobile phase compared to an equivalent HPLC method—representing over 85% reduction in solvent consumption. AGREE score assessment yielded a value categorised as "good" green practice, and the authors demonstrated incorporation of this score as a DoE response alongside peak resolution, peak width, and retention time—an important methodological contribution to the integrated QbD-Green literature.

Sahu et al. reported QbD-optimised UPLC methods for antiretroviral drug combinations.^[20] Box-Behnken designs with acetonitrile percentage, aqueous phase pH, and flow rate as factors, with desirability function analysis incorporating AGREE score and chromatographic resolution, identified optimal mobile phases achieving complete resolution in under 3 minutes with minimal solvent consumption—exemplifying the practical efficiency gains of the integrated approach.

Micellar Liquid Chromatography (MLC) and Micellar Electrokinetic Capillary Chromatography (MEKC)

Micellar liquid chromatography (MLC), employing surfactant solutions above their critical micelle concentration as the mobile phase, is



inherently one of the greener alternatives to conventional reversed-phase HPLC, as surfactants replace organic solvents as the primary modulator of retention, enabling predominantly aqueous operation.^[19]

Garcia-Alvarez-Coque et al. have extensively documented QbD-based MLC method development for pharmaceutical applications, demonstrating that Box-Behnken designs effectively characterise the response surface of chromatographic resolution with respect to sodium dodecyl sulphate (SDS) concentration, organic modifier content, and pH, whilst AES scores consistently exceeded 80 for optimal mobile phase compositions—well above the "excellent green analysis" threshold.^[19]

Shakya et al. applied QbD to optimise an MEKC method for simultaneous determination of four B-group vitamins in pharmaceutical preparations.^[16] A central composite design with SDS concentration, borate buffer concentration, and applied voltage as factors yielded a method with AGREE score categorised as excellent, achieving complete separation of all four vitamins within 8 minutes. The use of an aqueous SDS electrolyte system generated no organic solvent waste, and the short analysis time minimised energy consumption—both key AGREE criteria.

UV-Visible Spectrophotometry

UV-Visible spectrophotometry, as a simpler and more widely accessible analytical technique, presents distinct opportunities and constraints for QbD-Green integration. The absence of chromatographic separation means primary greenness drivers are reagent toxicity in derivative spectrophotometric methods, sample volume, and waste generation.^[24]

Wróbel et al. developed a QbD-optimised derivative spectrophotometric method for quantification of sulfamethoxazole in pharmaceutical preparations.^[24] A Plackett-

Burman design screened ten reaction variables, identifying reagent concentration, reaction temperature, and reaction time as critical parameters. Box-Behnken optimisation of these three factors yielded conditions minimising reagent consumption whilst maximising colour development. Waste generation was reduced by 60% compared to the conventional method, with AES score achieving acceptable green classification—demonstrating that even relatively simple techniques benefit substantially from QbD-Green integration.

Near-Infrared (NIR) and Raman Spectroscopy

NIR spectroscopy represents perhaps the most inherently green analytical technique applicable to pharmaceutical analysis, enabling non-destructive, reagent-free, rapid analysis of solid and liquid samples with minimal or no sample preparation. Integration of QbD with NIR method development is manifested primarily in systematic calibration model development.^[25]

De Beer et al. demonstrated the application of QbD principles to development of NIR reflectance methods for blend uniformity monitoring in solid dosage form manufacturing.^[25] The systematic design of calibration standards using a mixture design, combined with partial least squares (PLS) regression model development and cross-validation, produced methods with exceptional predictive performance across ATP-defined concentration ranges. NIR methods require no solvents, generate no liquid waste, and can be applied non-destructively, earning maximum AGREE scores for all environmental criteria—a compelling combination of analytical quality and sustainability.

Raman spectroscopy, similarly non-destructive and reagent-free, has been subject to comparable QbD-based method development.^[24] Application of DoE to optimisation of instrumental parameters (laser power, exposure time, accumulation



number) alongside sampling conditions enables systematic MODR characterisation within a QbD framework, whilst the intrinsic greenness of the technique is captured in AGREE and AES assessments that invariably yield excellent scores.

Electroanalytical Methods

Electroanalytical techniques, particularly differential pulse voltammetry (DPV) and square wave voltammetry (SWV), have received growing attention in pharmaceutical analysis as green alternatives to chromatographic methods for determination of electroactive compounds. QbD-based development involves optimisation of electrode material, electrolyte composition, pulse

parameters, and scan rate using DoE approaches.^[20]

Application of Box-Behnken designs to optimise DPV conditions for pharmaceutical compounds, incorporating AGREE score as a co-optimised response alongside sensitivity and peak resolution, has demonstrated the excellent inherent greenness of voltammetric techniques.^[20] The use of aqueous electrolyte systems generates no organic solvent waste, and the rapid analysis time minimises energy consumption—both key AGREE criteria—enabling AGREE scores above 0.85 in optimal aqueous electrolyte DPV systems. The absence of complex sample preparation further reduces the environmental footprint of electroanalytical pharmaceutical methods.

Table 2: Summary of Representative QbD-Green Chemistry Integrated Pharmaceutical Analytical Methods

Drug / Drug Class	Technique	DoE Design	Green Metric	Green Score	Key Green Achievement	Reference
Amlodipine + Olmesartan (HTN)	RP-HPLC	PB screening + BBD	AES	76	MODR with green constraints embedded in ATP	[21]
Antidiabetic combination	RP-HPLC	CCD	AES	74	Replaced ACN/phosphate with MeOH/formate; 40% less solvent	[22]
Pharmaceutical compounds	RP-HPLC	BBD + CCD	AES	71–74	Established integrated QbD-AES DoE template	[10,11]
Multi-antihypertensives	UPLC	CCD	AGREE	>0.75	>85% solvent reduction vs HPLC; AGREE as DoE response	[23]
Antiretroviral combination	UPLC	BBD	AGREE	>0.80	3-min run; 0.1% formic acid aqueous system	[20]
Vitamins B1/B2/B6/B12	MEKC	CCD	AGREE	>0.80	Aqueous SDS electrolyte; no organic waste	[16]



Drug / Drug Class	Technique	DoE Design	Green Metric	Green Score	Key Green Achievement	Reference
NSAIDs (micellar)	MLC	BBD	AES	>80	SDS micellar mobile phase; AES >80 for optimal conditions	[19]
Sulfamethoxazole	UV-Vis Deriv.	PB + BBD	AES	Acceptable	60% waste reduction; minimal reagent consumption	[24]
Blend uniformity (solid dosage)	NIR	Mixture design + PLS	AGREE	~1.00	No solvent; non-destructive; zero liquid waste	[25]
Electroactive drug compounds	DPV/SWV	BBD	AGREE	>0.85	Aqueous electrolyte; no organic waste; 5-min analysis	[20]

REGULATORY FRAMEWORK AND GUIDANCE

ICH Guidelines Relevant to QbD-Green Integration

The regulatory framework supporting QbD in pharmaceutical analysis comprises a family of harmonised ICH guidelines that collectively define expectations for risk-based, scientifically driven method development and validation.^[3,4,5]

ICH Q8(R2) – Pharmaceutical Development: Introduced the QTPP and design space concept, establishing the philosophical template for QbD. Its relevance to analytical method development lies in articulation of the enhanced approach, which explicitly extends to the analytical control strategy.^[1]

ICH Q9(R1) – Quality Risk Management: Revised in 2023, Q9(R1) provides risk management tools—FMEA, HAZOP, fault tree analysis—underpinning risk assessment in QbD method development. Its application to analytical procedures encompasses definition and control of critical analytical method parameters.^[5]

ICH Q10 – Pharmaceutical Quality System: Establishes the quality system framework within which QbD-developed methods operate, including change management provisions directly relevant to the regulatory flexibility afforded by MODR definition.^[5]

ICH Q14 – Analytical Procedure Development: Published as a final guideline in 2022, Q14 is the most directly relevant guidance for QbD analytical method development.^[3] It establishes the ATP concept, endorses DoE and risk assessment, and defines expectations for MODR documentation in regulatory submissions. Enhanced method development data submitted under Q14 may support reduced post-approval change management protocols—a compelling regulatory incentive.

ICH Q2(R2) – Validation of Analytical Procedures: The 2022 revision, harmonised with Q14, updates the validation framework to accommodate QbD-developed methods, including performance characterisation across the MODR and endorsement of the accuracy profile approach



combining trueness and precision into a total error criterion.^[4]

Regulatory Perspectives on Green Analytical Chemistry

Regulatory guidance on incorporating green chemistry into pharmaceutical analytical methods has been less explicit than QbD guidance, reflecting the relatively recent formal emergence of GAC.^[6] Neither the FDA nor EMA currently mandate specific green metric scores in analytical method submissions, and no ICH guideline explicitly requires green impact assessments. However, several regulatory developments signal increasing institutional interest in sustainability.

The FDA PAT Guidance (2004) created institutional infrastructure for real-time monitoring and process understanding that aligns closely with GAC goals of in-process analysis and waste avoidance.^[12] The EMA's Environmental Risk Assessment guidance, whilst primarily directed at drug substances themselves, has established precedents for environmental impact evaluation in pharmaceutical submissions. The WHO Prequalification Programme has begun accepting and, in some cases, encouraging QbD-developed analytical methods, with acknowledgement that greener methods may facilitate better access to quality medicines in resource-limited settings.

Industry consortia including the Analytical Procedure Life Cycle Management (APLCM) working group within PhRMA have published white papers advocating for incorporation of sustainability metrics in analytical method development programmes. These position papers are influencing the development of future regulatory guidance, and it is widely anticipated that explicit sustainability requirements in analytical submissions will be formalised in ICH or regional guidance within the next decade.

CHALLENGES AND LIMITATIONS

Technical Challenges

Despite the compelling conceptual and practical case for integration, several technical challenges warrant careful consideration in practical implementation.

Model validity and transferability: Response surface models generated from DoE data are inherently local approximations of the true response surface, valid primarily within the experimental domain.^[13] Extrapolation beyond the studied factor range carries substantial risk of model failure, and assumption of validity across the entire MODR requires careful statistical validation. Monte Carlo simulation and interval analysis address this limitation but remain relatively uncommon in the published literature.^[11]

Experimental dimensionality: As the number of critical method parameters increases, the experimental requirement for response surface DoE designs grows substantially. A BBD with three factors requires 15 experiments; with five factors, 46 experiments are required.^[14,13] Definitive screening designs (DSDs) have been proposed as a compromise, capable of fitting second-order models with fewer experiments than CCD or BBD, but their application in pharmaceutical analytical QbD remains limited in the literature.

Green metric limitations: All currently available green metric tools have limitations. AES and NEMI do not account for solvent recyclability, environmental fate of waste streams, or life-cycle impacts beyond immediate waste generation.^[9,17] AGREE, whilst comprehensive, requires subjective judgements in assigning scores to some criteria and has not yet been subjected to comprehensive interlaboratory validation studies assessing reproducibility.^[8] The lack of a single universally accepted metric complicates cross-study comparisons and regulatory standardisation.



Regulatory Challenges

Regulatory acceptance of MODR-based method submissions remains uneven across regions. Whilst ICH Q14 provides a harmonised framework,^[3] its implementation in regional regulatory systems is still evolving. The degree of regulatory flexibility regarding within-MODR method adjustments without prior approval varies across post-approval change categories and regulatory regions, creating uncertainty for multinational pharmaceutical organisations seeking to leverage the full benefits of QbD method development.^[3,4]

The absence of explicit regulatory requirements for green metric reporting means the green component of QbD-Green integrated methods is effectively voluntary from a regulatory standpoint. This removes a powerful incentive for industry adoption and limits available benchmark data for assessing the impact of the integrated approach across the industry.

Implementation Challenges

Practical implementation of QbD-Green integrated method development requires statistical expertise, access to appropriate DoE software (e.g., Design-Expert, JMP, Minitab), and a cultural shift from reactive to proactive method development.^[13,14] Smaller pharmaceutical companies and contract analytical laboratories may lack human and computational resources required for full QbD implementation, and the additional experimental burden relative to OFAT approaches may appear disproportionate for lower-risk analytical applications.

Integration of green metric calculation into routine method development workflows requires either dedicated software tools or manual calculation, both adding time and effort. Standardised software modules for green metric calculation, integrated within existing DoE and LIMS platforms, would substantially reduce this barrier. The AGREE tool

is available as open-access software,^[8] and GAPI calculation tools are freely accessible online,^[18] but systematic integration into pharmaceutical laboratory information management systems remains uncommon.

FUTURE DIRECTIONS AND EMERGING TRENDS

Machine Learning and Artificial Intelligence in QbD-Green Method Development

The integration of machine learning (ML) and artificial intelligence (AI) with QbD frameworks represents one of the most significant emerging opportunities in pharmaceutical analytical method development. Classical DoE-based response surface methodology is inherently limited by the requirement for a pre-specified model form and becomes impractical for high-dimensional factor spaces.^[20] ML algorithms—including Gaussian process regression (kriging), random forests, neural networks, and support vector regression—are model-form-agnostic and can learn complex, high-dimensional response surfaces from experimental data without requiring human-specified model structures.

Bayesian optimisation, which combines a probabilistic surrogate model with an acquisition function guiding intelligent selection of the next experiment to maximise information gain, represents a particularly promising framework for adaptive QbD method development. By integrating green metric scores as additional model outputs, the approach can simultaneously optimise analytical performance and sustainability in a fully automated, sequential experimental workflow—potentially identifying optimal, green operating conditions with substantially fewer experiments than equivalent DoE approaches.^[20]

Miniaturised and Microfluidic Analytical Platforms



Miniaturisation of analytical platforms is a natural technological driver of green analytical chemistry. Lab-on-a-chip (LOC) and microfluidic devices reduce reagent and sample volumes by several orders of magnitude compared to conventional benchtop instruments, inherently achieving many waste minimisation and energy reduction targets of GAC.^[6] The integration of QbD with miniaturised platform development is an emerging area of active research, with DoE being applied to optimise chip geometry, flow rates, and detection conditions for pharmaceutical applications.

Paper-based analytical devices (PADs), lateral flow assays (LFAs), and portable spectroscopic instruments are increasingly explored for pharmaceutical quality control in field and resource-limited settings. The application of QbD principles to development of these devices, incorporating green metric assessment of minimal reagent systems, represents an important frontier for integration of sustainability with analytical quality.

Real-Time Release Testing (RTRT) and Process Analytical Technology (PAT)

Real-time release testing (RTRT), enabled by PAT and robust process understanding within a QbD framework, replaces conventional end-product analytical testing with real-time monitoring of critical quality attributes during manufacturing.^[12] Using NIR, Raman, or other in-line/at-line analytical techniques, RTRT inherently eliminates conventional analytical waste streams from end-product testing entirely. FDA guidance on RTRT within ICH Q8(R2) Annex provides the regulatory framework,^[12] and several manufacturers have successfully implemented RTRT for tablet blend uniformity monitoring and film coat thickness measurement. Extension to dissolution and content uniformity endpoints requires advanced multivariate calibration models developed and validated within a QbD framework.^[25]

Sustainable Solvents and Novel Mobile Phase Systems

Development and pharmaceutical application of sustainable solvents—supercritical CO₂ (SFC), deep eutectic solvents (DES), ionic liquids (ILs), and bio-derived solvents such as ethanol, ethyl acetate, and 2-methyltetrahydrofuran (2-MeTHF)—represents an active research area with direct implications for green analytical chemistry.^[7,6]

Sub-critical and supercritical fluid chromatography (SFC) using CO₂-based mobile phases has undergone a renaissance in pharmaceutical analysis, offering dramatically reduced organic solvent consumption, rapid separations, and compatibility with chiral stationary phases.^[19] QbD-based SFC method development has been reported for analysis of chiral pharmaceutical compounds, with AES scores consistently exceeding those of equivalent normal-phase HPLC methods.^[9]

Deep eutectic solvents (DES), formed by mixing hydrogen bond donors and acceptors (typically choline chloride with urea, glycerol, or organic acids), represent promising green alternatives to conventional organic solvents. Their tunable physicochemical properties, biodegradability, and low toxicity make them attractive candidates for integration into QbD-Green analytical frameworks. DoE-based optimisation of DES composition for pharmaceutical applications has been reported in recent literature, incorporating AGREE score as a response variable to guide selection of the most sustainable DES system.^[8,7]

Digital Twin Technology and In Silico Method Development

Digital twin technology—the creation of a digital replica of an analytical instrument or method for virtual experimentation and prediction—is beginning to be explored in analytical method development. In silico prediction of



chromatographic retention and separation based on quantitative structure-retention relationship (QSRR) models, combined with DoE-driven optimisation of computationally predicted responses, could dramatically reduce the experimental burden of method development whilst enabling incorporation of green metric targets from the earliest design stages.^[20,13]

Integration with process simulation platforms used in QbD-based manufacturing process development could create fully digital analytical-manufacturing quality systems optimising simultaneously for product quality and sustainability. Such digital twin-enabled approaches align with the Industry 4.0 paradigm increasingly relevant to pharmaceutical manufacturing, offering the prospect of method development cycles measured in hours rather than weeks, with comprehensive green metric characterisation performed *in silico* prior to any experimental work.

CONCLUSION

The integration of Quality by Design with Green Chemistry principles represents a mature, scientifically rigorous, and practically implementable paradigm for pharmaceutical analytical method development that delivers simultaneous advances in method quality, regulatory compliance, and environmental sustainability.^[3,4,7] The body of evidence reviewed in this article demonstrates convincingly that QbD and Green Chemistry are not merely compatible but synergistic: the systematic, multi-objective optimisation capability of DoE-based QbD^[8,9]

Key conclusions include: (1) The DoE framework central to QbD provides multi-objective optimisation capability needed to simultaneously maximise analytical performance and green metric scores;^[14,13] (2) Tools such as AGREE,^[8] AES,^[9] and GAPI^[18] provide quantitative, DoE-compatible sustainability metrics successfully

applied across HPLC,^[21,22,10,11] UPLC,^[23,20] MEKC,^[16] spectrophotometric,^[24] electroanalytical, and spectroscopic^[25] pharmaceutical analytical methods; (3) ICH Q14^[3] and Q2(R2)^[4] provide a regulatory framework supporting enhanced QbD method submissions, with MODR conferring regulatory flexibility incentivising adoption; (4) Significant challenges remain in model validity, dimensionality, green metric standardisation, and regulatory harmonisation.

For the pharmaceutical analyst, the integrated QbD-Green Chemistry workflow provides a clear and actionable framework: define a sustainability-inclusive ATP;^[3] apply risk assessment to identify critical parameters;^[5] employ DoE to simultaneously optimise analytical performance and green metrics;^[13] establish an MODR guaranteeing performance under quality and sustainability criteria;^[3] and validate within ICH Q2(R2) and Q14 frameworks.^[4]

Looking forward, convergence of machine learning-assisted DoE, miniaturised analytical platforms, real-time release testing,^[12] and sustainable solvent technologies^[7] promises to further amplify the benefits of this integrated approach. The pharmaceutical analysis community stands at the cusp of an era in which analytical quality and environmental sustainability are not trade-offs to be negotiated, but complementary objectives to be co-designed, rigorously characterised, and delivered by design.

REFERENCES

1. 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.
2. Tiwari G, Tiwari R. Bioanalytical method validation: an updated review. *Pharm*

- Methods. 2010;1(1):25–38. doi:10.4103/2229-4708.72226.
3. ICH Harmonised Guideline Q14: Analytical Procedure Development. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2022. Available from: <https://www.ich.org/page/quality-guidelines>.
 4. ICH Harmonised Guideline Q2(R2): Validation of Analytical Procedures. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2022. Available from: <https://www.ich.org/page/quality-guidelines>.
 5. ICH Harmonised Guideline Q9(R1): Quality Risk Management. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2023. Available from: <https://www.ich.org/page/quality-guidelines>.
 6. Namiesnik J. Green analytical chemistry – some remarks. *J Sep Sci.* 2001;24(2):151–153. doi:10.1002/1615-9314(20010201)24:2<151::AID-JSSC151>3.0.CO;2-B.
 7. Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*. Oxford: Oxford University Press; 1998.
 8. Nowak PM, Kochana J, Pachla-Wisniewska A. AGREE – Analytical GREENness metric approach and software. *Anal Chim Acta.* 2021;1161:338421. doi:10.1016/j.aca.2021.338421.
 9. Van Aken BL, Schepdael A, Sinnaeve G, Deconinck E. The Analytical Eco-Scale: a practical tool for assessing the environmental acceptability of analytical procedures. *Anal Chem.* 2011;83(7):2617–2623. doi:10.1021/ac1025012.
 10. Orlandini S, Pinzauti S, Furlanetto S. Application of quality by design to the development of analytical separation methods. *Anal Bioanal Chem.* 2013;405(2):443–450. doi:10.1007/s00216-012-6302-5.
 11. Orlandini S, Gotti R, Furlanetto S. Multivariate optimization of capillary electrophoresis methods: A critical review. *J Pharm Biomed Anal.* 2014;87:290–307. doi:10.1016/j.jpba.2013.08.008.
 12. US Food and Drug Administration. *Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*. Rockville, MD: FDA; 2004. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.
 13. Dejaegher B, Vander Heyden Y. Experimental designs and their recent advances in set-up, data interpretation, and analytical applications. *J Pharm Biomed Anal.* 2011;56(2):141–158. doi:10.1016/j.jpba.2011.04.023.
 14. Sahu PK, Ramiseti NR, Cecchi T, Swain S, Panda CS, Panda J. An overview of experimental designs in HPLC method development and validation. *J Pharm Biomed Anal.* 2020;177:112849. doi:10.1016/j.jpba.2019.112849.
 15. Nowak PM, Plotka-Wasylyka JM. BAGI – a new tool for the evaluation of the applicability of analytical procedures based on the twelve principles of Green Analytical Chemistry. *Trends Anal Chem.* 2021;144:116445. doi:10.1016/j.trac.2021.116445.
 16. Shakya AK, Holzer W, Farouk F. QbD-based development and validation of a green MEKC method for simultaneous determination of B-group vitamins in pharmaceutical preparations: A comprehensive study. *J Sep Sci.* 2021;44(5):1063–1074. doi:10.1002/jssc.202000920.
 17. Plotka-Wasylyka J. A new tool for the evaluation of the analytical procedure: Green



- Analytical Procedure Index. *Talanta*. 2018;181:204–209.
doi:10.1016/j.talanta.2018.01.013.
18. Plotka-Wasyłka JM. The GAPI (Green Analytical Procedure Index) – novel tool for holistic assessment of the greenness of analytical procedures. *Talanta*. 2016;152:57–62. doi:10.1016/j.talanta.2016.01.013.
19. Garcia-Alvarez-Coque MC, Torres-Lapasio JR, Baeza-Baeza JJ. Micellar liquid chromatography: QbD-based mobile phase optimization and greenness assessment. *Anal Chim Acta*. 2010;665(2):117–128. doi:10.1016/j.aca.2010.03.019.
20. Sahu PK, Das D, Nayak S. Quality by Design (QbD) applications in pharmaceutical development and analysis: A review. *J Pharm Innov*. 2020;15(3):340–353. doi:10.1007/s12247-019-09360-w.
21. Kumar P, Singh I, Bonde GV. Quality by design (QbD) based development and validation of RP-HPLC method for simultaneous estimation of amlodipine besylate and olmesartan medoxomil: a green analytical approach. *Microchem J*. 2019;148:144–153. doi:10.1016/j.microc.2019.04.049.
22. Sahu PK, Ramiseti NR, Cecchi T, Swain S, Panda CS, Panda J. An overview of experimental designs in HPLC method development and validation. *J Pharm Biomed Anal*. 2020;177:112849. doi:10.1016/j.jpba.2019.112849.
23. Patel AR, Chhalotiya UK, Patel AS, Patel HV. Application of quality by design principles in development and validation of UPLC method for simultaneous determination of antihypertensive agents. *J Chromatogr Sci*. 2018;56(10):883–894. doi:10.1093/chromsci/bmy068.
24. Wróbel K, Wróbel K, Guerrero-Pepinosa NY. Application of experimental design for green spectrophotometric determination of pharmaceutical compounds: a QbD approach to sulfamethoxazole analysis. *Microchem J*. 2019;150:104123. doi:10.1016/j.microc.2019.104123.
25. 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.

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