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

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Review Article

Eco-Friendly Analytical Methods for Quantitative Estimation: A Critical Review of Green and White Analytical Chemistry Approaches in Pharmaceutical Analysis

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ARTICLE INFO

Published: 12 July. 2026

Keywords:
Green Analytical Chemistry; Eco-Friendly Methods; AGREE; GAPI; White Analytical Chemistry; Quantitative Estimation; HPLC

DOI:
10.5281/zenodo.21314278

ABSTRACT

Green Analytical Chemistry (GAC) has matured from a conceptual add-on into a quantifiable design criterion for methods used in the quantitative estimation of pharmaceuticals. Over the past decade, more than ten distinct greenness-assessment tools have emerged — from the qualitative National Environmental Method Index (NEMI, 2008) to fully quantitative, software-assisted metrics such as AGREE (2020), AGREEprep, Complex-GAPI, the Analytical Method Greenness Score (AMGS), and the 2024–2025 generation of tools including MoGAPI and the Analytical Green Star Area (AGSA). In parallel, White Analytical Chemistry (WAC) and complementary indices such as BAGI have emerged to balance environmental greenness against analytical performance and practicality ("Red" attributes), recognizing that a method optimized purely for greenness can sacrifice sensitivity or robustness. This review synthesizes the 2020–2025 literature on eco-friendly quantitative-estimation methods for pharmaceuticals, compares the principal greenness-assessment tools on their scoring logic and known limitations, and surveys recent applications combining Design of Experiments/AQbD optimization with green-solvent selection in HPLC-based quantitative estimation. Persistent gaps are identified in tool standardization, integration of greenness scoring into formal AQbD control strategies, and consistent joint reporting of green and white metrics.

INTRODUCTION

Quantitative estimation of active pharmaceutical ingredients — whether by HPLC, UV-spectrophotometry, or capillary electrophoresis — has historically prioritized sensitivity, precision, and regulatory-guideline compliance, with the environmental footprint of the method (solvent volume and toxicity, energy consumption, waste generation) treated as a secondary concern. Green

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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.

Analytical Chemistry reframes this priority list, applying the twelve principles first articulated by Gałuszka, Konieczka and Namieśnik to analytical method design: minimizing sample and reagent quantities, replacing hazardous solvents, reducing energy consumption, and enabling automation and miniaturization, without compromising the method's fitness for its intended quantitative purpose.

Because 'greenness' is otherwise a qualitative judgment, a series of assessment tools has been developed to make it measurable and comparable across methods. This review surveys that toolkit and its recent (2020–2025) evolution, and synthesizes how it is being applied specifically to quantitative-estimation methods for pharmaceutical actives, including combination methods optimized jointly for greenness and Analytical Quality by Design (AQbD) robustness.

2. Relevance and Regulatory Context

Interest in green analytical chemistry has accelerated sharply in the 2024–2025 literature window, with a recent comprehensive review identifying ten distinct greenness-assessment tools developed or substantially updated in 2024 and 2025 alone, reflecting recognition that earlier tools such as the Analytical Eco-Scale and GAPI, while useful, produced results that depended heavily on user interpretation and could not account for method performance or automation potential. This has driven development of software-assisted, more objective tools intended to guide method design proactively rather than merely score it retrospectively. The parallel emergence of White Analytical Chemistry and the BAGI (Blue Applicability Grade Index) metric reflects a maturing recognition that environmental greenness must be balanced against analytical practicality, cost, and performance rather than pursued in isolation — directly relevant to any laboratory now expected to report the environmental profile of a quantitative-estimation method alongside its ICH Q2(R2) validation data.

3. Greenness-Assessment Toolkit: A Comparative Overview

The following table summarizes the principal greenness-assessment tools referenced in the current literature, in approximate order of introduction.

Tool	Introduced	Character / Known Limitation
NEMI	2008	Qualitative pass/fail pictogram; low resolution between methods
Analytical Eco-Scale	2012	Quantitative penalty-point scoring; cannot localize the source of a poor score
GAPI	2018	Color-coded pentagram covering full workflow; semi-quantitative, interpretation-dependent
AGREE	2020	Software-assisted; integrates all 12 GAC principles into a single 0–1 score with visual clock-face output
Complex-GAPI / MoGAPI	2021 / 2024	Extends GAPI to pre-analytical steps; MoGAPI adds a dedicated scoring system and software
BAGI	~2023	White Analytical Chemistry metric; complementary to GAC tools, balancing greenness with applicability
AGSA	2025	Analytical Green Star Area; newer visual/quantitative hybrid tool
CACI	2024–2025	Click-chemistry-inspired; broader practical-applicability lens beyond environmental sustainability alone

4. Literature Review: Applications to Quantitative Estimation

A comprehensive 2024–2025 review examined ten greenness-assessment tools in depth, concluding that earlier tools such as the Analytical Eco-Scale and GAPI, despite wide adoption, remain retrospective and subjective, creating a gap between sustainability principles and their proactive use during method design — a gap the review argues newer software-assisted tools are intended to close.

A review of green approaches in HPLC for sustainable food analysis demonstrated GAPI's practical utility in distinguishing high- and low-impact HPLC procedures for paclitaxel quantitation, identifying solvent choice and detection mode as the key differentiating factors, and traced the evolution from GAPI to Complex-GAPI and MoGAPI for more granular, software-comparable assessment.

Within pharmaceutical quantitative estimation specifically, an eco-friendly HPLC-PDA method was developed and validated for the simultaneous determination of glibenclamide, metoprolol tartrate, and phenol red, optimized for trueness, precision, and robustness under ICH guidelines alongside its environmental profile — illustrating direct integration of greenness assessment into a routine multi-analyte quantitative method.

Combining AQbD optimization with green-chemistry principles, a harmonized Design of Experiments framework integrating green and white analytical chemistry was applied to synchronous chromatographic assay of anti-diabetic drug combinations (Prajapati et al.), and a stability-indicating RP-HPLC method for a fixed-dose combination explicitly built green chemistry into its AQbD development and validation (RSC Sustainability, 2026) — both demonstrating that eco-friendly design and AQbD robustness are increasingly treated as joint, not competing, objectives in quantitative-estimation method development.

5. Identified Gaps and Novelty Statement

Three gaps recur across the literature surveyed. First, despite the proliferation of greenness-assessment tools, no single tool has become a reporting standard; papers vary widely in which of NEMI, Eco-Scale, GAPI, AGREE, or the 2024–2025 tools (MoGAPI, AGSA, CACI) they apply, limiting cross-study comparability of 'how green' a given quantitative-estimation method actually is. Second, joint reporting of a green metric alongside a white/applicability metric such as BAGI remains uncommon in pharmaceutical quantitative-estimation papers, despite growing recognition that greenness and analytical performance must be reported together to avoid rewarding methods that are green but impractical. Third, formal integration of greenness scoring into the AQbD control strategy — rather than as a post-hoc addendum calculated after the method is already finalized — remains the exception rather than the rule.

6. CONCLUSION

Eco-friendly analytical method development for quantitative estimation has moved from a niche concern to an actively tooled, increasingly standardized discipline, with more than ten greenness-assessment metrics now available and a clear 2024–2025 trend toward software-assisted, less subjective scoring. The literature reviewed here shows growing — but still inconsistent — integration of green and white analytical chemistry metrics into mainstream quantitative-estimation method development, and an emerging but not yet routine practice of building greenness directly into the AQbD control strategy alongside conventional ICH Q2(R2) validation. Standardizing tool selection and formalizing joint green/white

reporting represent the principal opportunities for future work in this area.

Conflict of Interest

The authors declare no conflict of interest.

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HOW TO CITE: Dr. Rahul solunke*, Dappadwad Priyanka, Eco-Friendly Analytical Methods for Quantitative Estimation: A Critical Review of Green and White Analytical Chemistry Approaches in Pharmaceutical Analysis, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 2322-2325. https://doi.org/10.5281/zenodo.21314278