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GREEN ANALYTICAL CHEMISTRY IN PHARMACEUTICAL QUALITY CONTROL: A CRITICAL REVIEW OF GREENNESS ASSESSMENT TOOLS, ANALYTICAL METHOD VALIDATION, AND REGULATORY INTEGRATION

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ABSTRACT

Pharmaceutical quality control (QC) relies on analytical procedures that must be accurate, precise, selective, robust and fit for their intended purpose. Conventional methods can, however, consume large quantities of hazardous organic solvents, generate chemical waste, demand energy-intensive instrumentation and expose analysts to occupational hazards. Green analytical chemistry (GAC) seeks to reduce these impacts without weakening the analytical evidence needed for decisions on identity, strength, purity and stability.

This critical review examines the principal greenness- and applicability-assessment tools and how they can be integrated with method development and validation in pharmaceutical QC. It covers the National Environmental Methods Index (NEMI), the Analytical Eco-Scale, the Green Analytical Procedure Index (GAPI) and ComplexGAPI, Analytical GREEnness (AGREE), AGREEprep, the Blue Applicability Grade Index (BAGI) and the RGB/white analytical chemistry model. Their assessment boundaries, scoring logic, data requirements and limitations are compared, and representative published pharmaceutical QC methods are tabulated with the greenness tools their authors applied.

Particular attention is given to the distinction between environmental greenness, analytical performance and practical applicability: a method may be environmentally preferable yet unable to meet a required impurity limit, or analytically excellent yet resource-intensive. ICH Q2(R2) and ICH Q14 provide the framework for validation and science- and risk-based procedure development; neither prescribes a greenness metric or threshold. A QC-oriented reporting framework is proposed

that pairs a transparent greenness assessment with validation evidence, applicability and an explicit statement of trade-offs.

No single metric captures environmental, occupational, analytical and operational dimensions together. For pharmaceutical QC, the most defensible practice is to use complementary tools, disclose assumptions, report measured resource and waste data where possible, and show that sustainability gains do not compromise fitness for purpose.

KEYWORDS: green analytical chemistry; pharmaceutical quality control; analytical method validation; AGREE; GAPI; Analytical Eco-Scale; BAGI; white analytical chemistry; ICH Q2(R2); ICH Q14.

1. INTRODUCTION

Analytical procedures support nearly every stage of the pharmaceutical product lifecycle: raw-material testing, in-process control, release testing, stability studies, impurity profiling, cleaning verification and investigation of out-of-specification results. The credibility of these decisions depends on procedures that are scientifically justified and appropriately validated. Historically, method selection has concentrated on analytical performance, throughput, cost and regulatory suitability. Environmental and occupational consequences, such as solvent toxicity and consumption, waste, energy demand and analyst exposure, have rarely been equally visible selection criteria.

Green analytical chemistry applies sustainability thinking to the whole analytical workflow. Its scope extends beyond replacing one solvent with another to sample collection, preservation, transport, preparation, extraction, separation, detection, data processing, cleaning and disposal. The twelve principles of GAC described by Gałuszka and colleagues encourage smaller sample and reagent quantities, safer chemicals, energy efficiency, direct analysis where feasible and waste prevention [1]. These principles are useful design objectives, but they do not by themselves give a reproducible numerical comparison between methods. Metrics were developed to make selected environmental attributes explicit.

The number of metrics has grown substantially. NEMI provides a compact hazard-oriented profile [2]; the Analytical Eco-Scale subtracts penalty points from an ideal score [3]; GAPI represents several stages of the analytical workflow [4]; and AGREE converts the twelve GAC principles into a weighted overall score and pictogram [5]. BAGI complements these by examining practical applicability rather than environmental impact [6]. Recent reviews catalogue many further metrics and stress that tools differ in scope, assumptions and outputs [7–10].

The central issue for pharmaceutical QC is not whether a method is labelled green. A QC method must meet its intended analytical purpose, including suitable specificity, accuracy, precision, range, sensitivity and robustness. A greener method that cannot detect a critical impurity at its reporting threshold is not an acceptable substitute. Conversely, an analytically excellent method that uses large

volumes of hazardous solvent is a candidate for improvement if a redesigned method preserves performance. Sustainable method development is therefore a constrained optimisation: reduce environmental burden while retaining or improving fitness for purpose.

This review examines the assessment tools most relevant to pharmaceutical analysis and how they can be built into method development, validation and lifecycle management under ICH Q2(R2) and Q14 [11,12]. Its intended contribution is a QC-oriented decision framework that separates three questions: (i) how environmentally burdensome is the procedure; (ii) does it meet the analytical requirements; and (iii) can it be implemented reliably in the intended laboratory?

2. Review scope and approach

This manuscript is a critical narrative review, not a systematic review. It synthesises the foundational papers on GAC principles and on each assessment tool [1–6,13–16], peer-reviewed reviews of metrics [7–10,17,18], reviews of green LC, CE and impurity analysis in pharmaceutical work [10,19,20], representative recent pharmaceutical QC methods (Section 6.6) and the official ICH Q2(R2) and Q14 guidelines [11,12].

Search used for this draft. Sources were identified through targeted web and bibliographic-database queries run on 29 October 2026, combining tool names (NEMI, Eco-Scale, GAPI, ComplexGAPI, AGREE, AGREEprep, BAGI, MoGAPI, RGB/white analytical chemistry) with pharmaceutical terms (pharmaceutical, tablet, impurity, stability-indicating, HPTLC, HPLC, capillary electrophoresis) and with ICH Q2(R2)/Q14. Bibliographic details were checked against publisher pages, PubMed records or institutional repositories. This was not an exhaustive, protocol-driven search; no record counts are reported and no PRISMA diagram is presented.

Suggested eligibility criteria. (1) English-language peer-reviewed research or review articles; (2) procedures relevant to pharmaceutical, biomedical or transferable QC applications; (3) a stated greenness or applicability assessment, or enough method detail for a defensible evaluation; (4) official guidelines when discussing validation or procedure development. Editorials without methods, duplicates and articles lacking analytical detail are excluded.

Because metrics use different input variables and scales, their numerical outputs are not treated as interchangeable. A score from one tool is never ranked against a score from another as if both measured the same construct; comparisons below are conceptual.

3. Green analytical chemistry in pharmaceutical QC

3.1 Sources of environmental and occupational burden

The footprint of a pharmaceutical analytical procedure is spread across its whole workflow. In liquid chromatography, mobile-phase preparation, equilibration and flushing may dominate solvent use, while extraction and clean-up add solvent and solid waste. In HPTLC, plate development, chamber saturation, derivatisation and plate disposal contribute. Spectrophotometric procedures often use less

solvent and simpler instruments, but may need large sample volumes, derivatising reagents or hazardous extraction solvents. An apparently low-solvent instrumental step can be preceded by intensive sample preparation.

Relevant dimensions include chemical hazard, reagent volume and mass, waste quantity and composition, energy, analysis time, sample size, number of preparation steps, automation, operator exposure and end-of-life handling. Their relative weight depends on the application. A solvent with lower acute toxicity is not automatically preferable on every endpoint: substitution should weigh toxicity, flammability, volatility, persistence, compatibility with analyte and instrument, and the quantity required.

3.2 Greener method-development strategies

Options include replacing highly hazardous solvents, reducing flow rate and run time, using shorter or more efficient columns, miniaturising extraction, reducing sample mass, avoiding unnecessary derivatisation, combining preparation steps, using direct or in-situ measurement where valid, and automating to improve reproducibility and reduce handling. Supercritical-fluid chromatography, capillary electrophoresis, micellar or fully aqueous LC and modern spectroscopic techniques may help in selected cases, but none is inherently green in every application [10,19]. Each must be judged against analyte chemistry, required detection limits, throughput, instrument availability and total workflow burden.

Greener solvents should be chosen from documented hazard and sustainability data, not from the label "green". Methanol, acetonitrile, ethanol, isopropanol, ethyl acetate and water differ in selectivity, viscosity, UV cut-off, miscibility, flammability, toxicity and waste-treatment implications. Ethanol, for example, has a UV cut-off near 210 nm and higher viscosity than acetonitrile; a substitution that lowers toxicity may raise back-pressure, analysis time or energy use [21]. These trade-offs should be measured where feasible and discussed openly.

3.3 The pharmaceutical QC constraint

A QC method is fit for purpose only if its performance is sufficient for the decision it supports. API assay, trace-level mutagenic impurity testing, dissolution, residual solvents and stability-indicating impurity profiling have very different selectivity and sensitivity requirements. A universal rule favouring the lowest solvent volume or highest greenness score is therefore scientifically inadequate. Greenness should be optimised only within the set of methods that satisfy the analytical target profile (ATP) and applicable compendial or regulatory requirements [12].

4. Major greenness and applicability assessment tools

No tool measures "greenness" as a single physical quantity; each operationalises a chosen subset of attributes within a chosen boundary [7,8,27]. The subsections below describe what each tool captures and where it misleads.

4.1 National Environmental Methods Index (NEMI)

NEMI summarises four criteria in a four-quadrant pictogram: whether reagents are persistent, bioaccumulative and toxic; whether any are hazardous; whether pH is corrosive; and whether waste exceeds a fixed threshold [2,7]. Its strength is simplicity, which makes it a reasonable first screen when method information is limited.

That simplicity is also its main weakness. Binary criteria hide gradations, so two procedures with very different solvent volumes or energy demands can receive the same pictogram. NEMI should not be used alone to claim that one complete pharmaceutical procedure is substantially greener than another.

4.2 Analytical Eco-Scale

The Analytical Eco-Scale starts from an ideal score of 100 and subtracts penalty points for reagent amount and hazard, energy, occupational exposure and waste [3]. Scores above 75 are conventionally described as excellent, 50–75 as acceptable and below 50 as inadequate [21]. The format is easy to communicate and shows which factors drive the penalty.

The result depends on the completeness of the reagent inventory and on how hazard categories, energy and waste are interpreted. A final number can conceal which component dominates. Authors should publish the penalty-point table and the method conditions behind it.

4.3 GAPI, ComplexGAPI and MoGAPI

GAPI uses a five-pentagram pictogram, coloured green, yellow or red, covering sample collection and preparation, reagents, instrumentation and waste [4]. Its advantage is workflow visibility: it shows where burdens arise. ComplexGAPI adds a hexagon for pre-analytical steps such as synthesis of sorbents or reagents [14], and MoGAPI (2024) adds a total numerical score to the GAPI pictogram [16].

The original GAPI does not rank methods numerically, and colour assignments can be subjective. The pictogram is only as complete as the procedure description: if preparation or waste details are omitted, it can appear more comprehensive than the underlying data.

4.4 Analytical GREEnness (AGREE)

AGREE converts each of the twelve SIGNIFICANCE principles into a 0–1 sub-score and combines them into an overall 0–1 score shown in a circular, twelve-segment pictogram [5]. Users can weight principles, and free software makes the calculation reproducible.

Weighting is not a neutral detail: different priorities change the overall result. Every AGREE score should be reported with software version, inputs, weights and enough method detail to reproduce it. AGREE is not a substitute for a solvent inventory, a life-cycle assessment, an occupational risk assessment or validation.

4.5 AGREEprep and sample-preparation metrics

Sample preparation can dominate the burden when extraction, clean-up, evaporation, reconstitution or derivatisation are involved. AGREEprep scores ten principles of green sample preparation on a 0–1

scale [13]. It is most useful when two methods share an instrument but differ in extraction volume, sample mass, step count or waste.

A preparation score is not a whole-method score. Where the instrumental stage consumes much solvent or energy, AGREEprep alone is incomplete; authors should state the boundary and pair it with a whole-procedure tool.

4.6 Blue Applicability Grade Index (BAGI)

BAGI evaluates practicality, not environmental greenness [6]. It scores ten attributes, including type of analysis, number of analytes, instrumentation, sample throughput, preparation, reagents, preconcentration, automation and sample amount, each at 2.5, 5.0, 7.5 or 10 points, giving a total from 25 to 100 [6,22]. This matters in QC, where a method must fit available instruments, analyst skills, sample load and turnaround time.

BAGI is complementary to, not competing with, a greenness metric. A high BAGI score does not show environmental superiority, and a high greenness score does not show practical readiness.

4.7 White analytical chemistry, RGB models and emerging metrics

The white analytical chemistry (WAC) concept combines red (analytical performance), green (environment and safety) and blue (practicality) dimensions in RGB-based models [15]. Since 2020 many further tools have appeared, including red performance indices, carbon-footprint and cost indices, and multidimensional frameworks [17]. These can help when their boundary matches the question.

The growth in metrics creates a comparability problem. A more elaborate score is not automatically more accurate; extra inputs improve coverage only if they are reliable, consistently defined and transparently reported. Tools should be chosen for the question asked, not because they are popular, and recent guidance on good evaluation practice should be followed [18].

4.8 Comparative summary

Tool	Main emphasis	Output	Strength	Limitation and recommended use
NEMI [2]	Four hazard and waste criteria	Four-quadrant pictogram	Fast, simple screen	Binary, low resolution; not for whole-method ranking
Analytical Eco-Scale [3]	Penalty points from an ideal 100	Numerical score	Shows which inputs are penalised; good within one study	Sensitive to inventory assumptions; publish the penalty table

Tool	Main emphasis	Output	Strength	Limitation and recommended use
GAPI / ComplexGAPI / MoGAPI [4,14,16]	Stages of the workflow (plus pre-analytical steps; plus total score)	Multi-part pictogram (MoGAPI adds a score)	Locates where burdens occur	Colour assignment subjective; needs complete workflow data
AGREE [5]	Twelve GAC principles	0–1 score and pictogram	Structured, weightable, software-supported	Weights and inputs change the score; report both
AGREEprep [13]	Ten principles of green sample preparation	0–1 score and pictogram	Makes extraction burden visible	Preparation only; pair with a whole-method tool
BAGI [6]	Practical applicability	25–100 score and pictogram	Addresses implementation in QC	Not a greenness score; use alongside a GAC metric
RGB / WAC tools [15,17]	Performance, greenness and practicality together	Colour or composite profile	Multidimensional summary	Tool-specific boundaries hinder cross-tool comparison

5. Greenness assessment and analytical method validation

5.1 Validation is not a greenness metric

Validation establishes that a procedure is suitable for its intended purpose; greenness assessment characterises selected environmental and safety attributes. These are different evaluations. A method can be fully validated yet environmentally burdensome, or appear green yet fail a required performance characteristic. Neither a high score nor a favourable pictogram demonstrates accuracy, specificity, precision or robustness.

ICH Q2(R2) gives the harmonised framework for validating analytical procedures, and ICH Q14 covers science- and risk-based development and lifecycle management [11,12]. Both were adopted at ICH Step 4 on 1 November 2023 [11,12]. The FDA announced both as final guidances on 7 March 2024, and the EMA set 14 June 2024 as their date of coming into effect [11,12,28]. The EMA versions record later error corrections (Q2(R2): 30 November 2023 and 4 April 2025; Q14: 4 April 2025), so authors should cite the current official version [11,12].

Neither guideline prescribes AGREE, GAPI, BAGI or any greenness threshold. Authors should therefore not describe a method as "ICH-validated for greenness". They should report the applicable validation evidence and the environmental assessment separately.

5.2 Linking green design to the analytical target profile

ICH Q14 describes the ATP as a statement of the intended purpose and required performance of a procedure [12]. Defining it before optimisation lets greenness be weighed only among candidates that can succeed. The ATP should state intended use, analyte and matrix, concentration range, decision

limits, required selectivity, expected throughput and performance criteria. Candidates that fail essential criteria are excluded before greenness is compared.

This sequence avoids selecting an environmentally attractive method that lacks detection capability. For impurity methods, shortening run time or changing the organic modifier may alter resolution of critical pairs. For assay methods, solvent substitution may change peak shape, retention, extraction recovery or detector response. Each change needs re-optimisation and re-evaluation of the affected validation characteristics.

5.3 Validation characteristics affected by greener redesign

Performance characteristic	Potential impact of green redesign	Evidence to report
Specificity / selectivity	New solvent, column chemistry, extraction or detection may alter interference and critical-pair resolution	Representative chromatograms or spectra; placebo, matrix and forced-degradation evaluation; peak purity where relevant
Accuracy / recovery	Smaller extraction volume or alternative solvent may change extraction efficiency and matrix effects	Recovery across relevant levels; full sample-preparation details
Precision	Miniaturisation and automation may change handling variability	Repeatability and intermediate precision appropriate to intended use
Range and response	New conditions can change detector response and working range	Calibration model, range justification, residuals
Detection / quantitation	Smaller sample or injection volume can lower signal-to-noise	Evidence that LOD/LOQ meet the decision limits
Robustness	Lower flow, shorter columns, new solvents or modified pH may increase sensitivity to small changes	Risk-based robustness study; control of critical method parameters [12]
System suitability / transfer	Greener method may need different limits or instrument configuration	Acceptance criteria, transfer evidence, operational controls

5.4 Validation and lifecycle management

Greenness is best treated as a development and lifecycle consideration, not a one-time badge. A laboratory can baseline a current method, identify its dominant burdens and evaluate redesign options under documented risk assessment. Any change to a validated method must be assessed for its effect on performance; depending on the change, partial or full revalidation, verification or comparability data may be needed. Q14 describes how established conditions and post-approval change management support such decisions [12].

The useful outcome is a traceable record of why the revised method is preferable, which requirements were assessed, what changed and which risks remain. A higher AGREE score is not proof of superior analytical quality; it must be read alongside validation and applicability evidence.

6. Application to common pharmaceutical QC techniques

6.1 HPLC and UHPLC

Reversed-phase HPLC is the workhorse for assay, related substances, dissolution and stability-indicating methods [19]. Its burden comes from organic mobile phase, column conditioning, gradient re-equilibration, flushing, sample preparation and mixed solvent waste. Improvements include lower flow where feasible, shorter or more efficient columns, optimised gradients, less flushing, smaller injection and preparation volumes, and less hazardous mobile phases such as ethanol-based systems [21].

These changes must be judged as a complete workflow. A shorter run may not reduce total solvent use if equilibration and washes stay long. Lower flow saves solvent but may lengthen analysis or alter peak shape. A less hazardous solvent can change selectivity or raise back-pressure. Report flow rate, run and equilibration times, mobile-phase composition, preparation volumes and waste per sample, and calculate every metric from the same defined workflow.

6.2 HPTLC

HPTLC can process many samples in parallel with low solvent per sample. Its profile depends on samples per plate, mobile-phase volume, chamber saturation, derivatisation, plate material, extraction and disposal. Comparisons with HPLC should use a common functional unit, such as a specified number of samples analysed to a defined performance requirement, not one plate against one injection. Parallel throughput is not by itself environmental superiority.

6.3 UV-visible spectrophotometry

UV-visible methods suit routine assay when the analyte absorbs well and the matrix does not interfere. They avoid large mobile-phase volumes, but hazardous extraction solvents, derivatising reagents or heavy preparation can make them no greener than an optimised chromatographic method. Direct measurement is appropriate only when specificity is adequate, and a simple method should not be called stability-indicating without supporting forced-degradation evidence.

6.4 Capillary electrophoresis and alternative separations

CE uses microlitre volumes of electrolyte and sample and can sharply reduce reagent consumption and waste [10]. It suits charged analytes when its selectivity and sensitivity meet the ATP. Suitability depends on robustness, capillary conditioning, buffer composition, detection, throughput and instrument availability; a complete comparison also counts analysis time, rinses, repeat runs and practical implementation.

6.5 Impurity profiling and stability-indicating procedures

Impurity analysis is where greenness and performance conflict most sharply, because low-level impurities need high selectivity and sensitive detection. A solvent substitution that reduces hazard but compromises critical-pair resolution is unacceptable, and a shorter run that causes co-elution or poor peak purity fails the purpose. Greener impurity methods must be assessed against impurity limits, specificity, degradation-product coverage and quantitation capability. A recent review of green

impurity determination covers greener chromatography, spectroscopy, microextraction and miniaturisation [20]; such literature informs candidate design, but each method must still be evaluated for its own analytes, matrix and limits.

6.6 Representative published pharmaceutical QC methods

The table below lists recent methods that report both validation and greenness assessment. Values were taken from the original article or its publisher abstract, as marked; scores are as reported by the original authors and were not recalculated. Scores from different tools are not comparable with one another.

Recent pharmaceutical QC methods reporting greenness and applicability assessment

Study	Analyte(s) and matrix	Technique and key conditions	Validation basis	Tools and reported results	Data checked from
Mansour et al. 2026 [21]	Imeglimin HCl with metformin impurity and degradants; tablets and dissolution	Ion-pair RP-HPLC, C8 150 × 4.6 mm; 0.1% octane sulfonate–ethanol 80:20; 1 mL/min; 8 min run	ICH Q2(R2); range 0.4–96.0 µg/mL; LOQ 0.679 µg/mL; forced degradation with PDA peak purity	Eco-Scale 81; MoGAPI 80; AGREE, CaFRI, BAGI and CACI reported as pictograms	Full text
Nassar et al. 2025 [22]	Favipiravir, molnupiravir, nirmatrelvir, remdesivir, ritonavir; tablets, capsules, infusion powder	RP-HPLC, C18 150 × 4.6 mm; water–methanol 30:70, pH 3.0; 1 mL/min; 6 min run	ICH; range 10–50 µg/mL; LOD 0.415–0.946 µg/mL; no forced degradation	AGREE 0.70; AGREEprep 0.59; MoGAPI 70; BAGI 82.5; CACI 79	Full text
Pregabalin–etoricoxib study 2025 [23]	Pregabalin and etoricoxib; tablets	Stability-indicating RP-HPLC	ICH Q2(R2)	AGREE 0.78; AGREEprep 0.62; GAPI and BAGI also applied	Publisher abstract
Dokewar et al. 2026 [25]	Olaparib impurities	RP-UHPLC developed by analytical QbD; about 4.5 mL solvent per run	AQbD with Monte Carlo risk assessment	AGREE 0.74; no red fields in GAPI	Publisher abstract
Trifluridine–tipiracil HPTLC 2025 [24]	Trifluridine and tipiracil; formulations	QbD-developed HPTLC	ICH Q2(R1); %RSD < 2%	AGREE 0.81; Eco-Scale 86; BAGI 80; ComplexGAPI applied	Publisher abstract

Study	Analyte(s) and matrix	Technique and key conditions	Validation basis	Tools and reported results	Data checked from
Paclitaxel method comparison 2025 [26]	Paclitaxel; published HPLC methods compared	Retrospective seven-tool comparison	Not applicable (comparison study)	Best Eco-Scale 90 and best BAGI 72.5 went to different methods	Publisher abstract

Three patterns stand out. First, authors increasingly report several tools, but tool sets differ, so results are hard to compare across papers. Second, validation depth varies: one of the five method papers still cites the superseded ICH Q2(R1), and the five-analyte method in [22] reports no forced-degradation study. Third, the paclitaxel comparison [26] shows that different tools can favour different methods, which supports reporting complementary tools rather than one score.

6.7 Worked example: per-injection solvent inventory

A metric score should rest on a measured or derivable inventory. Using only the conditions reported in [21] and [22], mobile-phase use per injection is flow × run time:

Method	Flow (mL/min)	Run (min)	Mobile phase per injection (mL)	Organic solvent per injection
Imeglimin ion-pair HPLC [21]	1.0	8	8.0	1.6 mL ethanol (20%)
Five-antiviral HPLC [22]	1.0	6	6.0	4.2 mL methanol (70%)

The shorter run does not mean lower organic consumption: the 6-min method uses about 2.6 times more organic solvent per injection, and a more hazardous one. Neither figure includes system-suitability and blank injections, the at-least-30-min equilibration reported in [22], or sample-preparation solvent (50 mL ethanol per tablet stock in [21]; methanol for all extraction and dilution in [22]). The methods have different purposes, so this is not a ranking; it shows why the functional unit and boundary must be stated. Authors should repeat this calculation with full per-batch inventories and enter the same inputs into AGREE, Eco-Scale and BAGI, archiving the software files.

7. Integrating greenness, applicability and analytical performance

A common weakness in method-comparison studies is using one score to imply overall superiority. Environmental burden, analytical performance and applicability are related but distinct, and the most defensible evaluation presents them separately before explaining the decision. AGREE or GAPI characterise environmental features; BAGI gives a view of practicality; validation data establish fitness for purpose. Measured resource data should accompany composite scores wherever available.

7.1 Proposed QC-oriented assessment framework

The framework below is a reporting aid for pharmaceutical QC studies. It is not a validated regulatory index and should not be presented as a new scoring algorithm unless its developers conduct a formal development and validation study.

Step	Action	Minimum evidence
1. Define intended use	Specify analyte, matrix, decision, range, throughput and target limits	ATP or method purpose statement [12]
2. Define assessment boundary	Include sampling, preparation, separation, detection, cleaning and waste as appropriate	Workflow diagram and method inventory
3. Screen analytical fitness	Keep only candidates that can meet essential requirements	Selectivity, sensitivity, accuracy, precision and robustness evidence as applicable
4. Quantify the footprint	Record solvent and reagent volumes, hazard classes, waste, energy and time	Raw inputs, assumptions and functional unit (per sample or per batch)
5. Apply complementary tools	One whole-method greenness tool; add a second only to answer a distinct question	AGREE or GAPI/MoGAPI, plus BAGI or AGREEprep where justified
6. Examine trade-offs	Identify whether a score is driven by hazard, volume, energy, preparation or other factors	Weight or sensitivity analysis with narrative interpretation
7. Document validation and implementation	Confirm performance, instrument compatibility, transfer needs and waste handling	Validation summary, system suitability, implementation constraints
8. Report reproducibly	Provide settings, software versions, calculation files and full method details	Supplementary tables, calculation inputs, version and date [18]

7.2 Functional unit and fair comparison

A fair comparison needs a consistent functional unit. "Per injection" can mislead if one procedure needs multiple extractions, repeat injections or long equilibration (Section 6.7). "Per reportable result meeting the required specification" is usually more meaningful in QC, provided workflow and performance are defined. For batch testing, reporting the footprint per batch and per accepted sample shows the effect of throughput and repeat analysis.

The boundary must be explicit. Counting mobile phase but excluding extraction favours preparation-heavy methods; excluding warm-up or cleaning understates energy and solvent. Full life-cycle assessment may exceed routine method development, but authors should state what was included and excluded.

7.3 Avoiding false precision

Composite scores can look more precise than their inputs justify. If volumes are estimated, hazard data incomplete or energy unmeasured, the assessment should say so. Avoid excessive decimal places and avoid declaring a universally "best" tool; a transparent account of data and assumptions is usually more useful than a rank order.

8. Critical gaps in the current evidence base

8.1 No harmonised boundaries. Metrics cover different parts of the workflow and different endpoints, which prevents direct comparison across tools and studies. A minimum reporting template for boundary, functional unit, inputs and omitted stages would help.

8.2 Dependence on user-entered assumptions. Many tools require the analyst to classify hazards, estimate volumes, choose weights or map steps to principles. Two users can obtain different results for the same method [18]. Papers should provide calculation sheets, not only a pictogram or final score.

8.3 Scores are not total sustainability. A greenness score may not capture upstream solvent manufacture, transport, instrument manufacture, water use, local waste-treatment capacity or full toxicity. It is more accurate to say a method performs favourably under a named metric and boundary than to call it sustainable.

8.4 Limited integration with routine QC. Greenness metrics are now common in method-development papers, but their use in routine method selection, change control and lifecycle management is uneven. Adoption needs clear responsibilities, reliable data collection, training and evidence that environmental gains do not compromise quality decisions.

8.5 Inconsistent validation reporting. Some green-method papers emphasise scores while giving limited detail on critical validation characteristics, matrix effects, robustness or transfer (Section 6.6). A method is not an improvement if its limitations cause repeat testing, extra confirmatory analysis or more invalid results.

8.6 Few prospective comparative studies. Most studies assess a new method after optimisation. More informative designs compare the existing routine method with the proposed alternative on the same functional unit, boundary and requirements, and report solvent and waste reduction, turnaround, repeat-test frequency, exposure controls and cost alongside validation.

9. Practical recommendations for authors and QC laboratories

- State the procedure's purpose and critical analytical requirements before discussing greenness.
- Choose tools by question: a whole-workflow greenness metric, a preparation-specific tool when relevant, and an applicability tool when implementation matters.
- Report the full workflow, including extraction, derivatisation, washing, conditioning and waste treatment, not just the instrument run.

- Use a consistent functional unit and state the boundary.
- Give actual solvent and reagent quantities per sample or batch, separating measured values from estimates.
- Report tool name, software version, date, weights, settings, hazard sources and calculations.
- Report validation separately and explain how each green modification could affect specificity, accuracy, precision, sensitivity, range or robustness.
- Cite the current version of ICH Q2(R2) and Q14, not Q2(R1).
- Do not use a greenness score as a substitute for regulatory compliance, validation or risk assessment.
- Discuss trade-offs and residual risks, including effects on selectivity, pressure, analysis time and instrument compatibility.
- Provide supplementary data for independent reproduction and avoid claims such as "completely green" or "environmentally harmless".

10. FUTURE PERSPECTIVES

Progress depends less on new scores than on better, more comparable data behind existing ones. A standardised reporting checklist could record purpose, functional unit, boundary, reagent and solvent quantities, hazard references, waste, energy, tool and version, validation evidence and implementation constraints. It would not require full life-cycle assessment but would make comparisons transparent; recent good-evaluation-practice proposals are a starting point [18].

Automated extraction of method parameters from papers and electronic laboratory records could reduce the effort of populating tools, provided systems preserve provenance, flag missing data and never silently assume unreported volumes or hazards. Machine-learning optimisation may suggest lower-solvent conditions, but recommendations must be confirmed experimentally and assessed for performance.

Sustainability can also be built into analytical quality by design. Critical method parameters could be assessed for their effect on both quality attributes and environmental burden, identifying operating regions that meet quality requirements while minimising solvent, energy and waste. This complements, and does not replace, the development and validation requirements of Q14 and Q2(R2) [11,12].

Finally, independent case studies applying several tools to the same pharmaceutical procedures should report how far tool rankings agree, how results shift with weights or boundaries, and whether the method-selection decision changes [26].

11. Limitations of this review

This is a critical narrative review, not a systematic review or meta-analysis. The tools use different domains and outputs, so their scores cannot be pooled without a defensible harmonisation method.

Literature was identified by targeted searches rather than a registered protocol; no formal risk-of-bias assessment was performed; and four of the six studies in Section 6.6 were checked at abstract level only. Scores in Section 6.6 are as reported by the original authors and were not independently recalculated.

12. CONCLUSION

Greenness assessment makes the environmental consequences of pharmaceutical analytical procedures more visible, but no single metric captures environmental impact, analytical performance and practical applicability together. NEMI, the Analytical Eco-Scale, GAPI and AGREE offer different views of environmental burden; preparation-specific tools clarify extraction impacts; and BAGI addresses applicability. Each output must be read against its boundary and input assumptions.

For pharmaceutical QC, environmental improvement must occur within the constraint of fitness for purpose. ICH Q2(R2) and Q14 frame validation and procedure development, while greenness metrics remain complementary sustainability assessments, not regulatory tests. A robust publication compares methods on a defined functional unit, discloses the full workflow and calculation inputs, reports validation separately and discusses trade-offs explicitly. The most credible route to sustainable pharmaceutical analysis is transparent, complementary assessment backed by reproducible data and demonstrated analytical performance.

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