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Article

Green-By-Design Pharmaceuticals: from Human Admet to Environmental Safety in AI-Enabled Sustainable Drug Discovery

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Abstract: Objectives to analyze how the concept of pharmaceutical sustainability could be taken further into the upstream processes of candidate selection to combine human ADMET, synthetic efficiency, environmental fate, ecotoxicity, biodegradability and AI without affecting therapeutic performance. This is a critical narrative review, which gave priority to peer-reviewed literature published 2021 to 30 August 2026 (with preference to 2024-2026) and the older foundational studies were retained. Official EMA, EUR-Lex, European Commission SSbD, OECD and PREMIER sources were added to PubMed search and targeted publisher searches. The study design, relevance of the endpoints, validation, transparency and relevance to an actionable R&D decision were evaluated, and no PRISMA flow or meta-analysis will be asserted. Prevention by design is supported, with an uneven maturity. Process metrics, solvent selection, catalysis, biocatalysis and continuous processing are relatively developed; prediction of PBT-related endpoints, bioaccumulation and ecotoxicity are being developed, but biodegradability prediction is less certain. The multi-objective prioritization can be assisted by AI when the domains of applicability, uncertainty, and experimental validation are clear. Out of the sources found, no prospective program could support the entire therapeutic-process-environmental framework in its entirety; instead, a stage-gated structure of evidence is suggested. The green reaction or environment score alone does not characterize a Green-by-Design pharmaceutical. It is a medically plausible therapy whose molecular characteristics, manufacturing burden and post consumption ecological conduct are taken into account as long as judgments are changeable. AI must not replace transparent evidence, regulatory assessment or validation but reveal trade-offs and focus on experiments.

Keywords: Green Chemistry, Sustainable Drug Discovery, Green-By-Design Pharmaceuticals, ADMET, Environmental Fate, Ecotoxicity, Biodegradability, Artificial Intelligence, Multi-Objective Optimization

Introduction

Medicines are made to react with biology; by-products that are emitted thus cannot be considered chemically inactive. Parent APIs and active metabolites can be discharged into wastewater systems to surface water, sediment, soil and biota. International surveillance has shown massive drug contamination of pharmaceuticals with possible ecotoxicological risk on a significant proportion of

sampled river sites [1,2]. However, occurrence only defines exposure as opposed to harm: ecological risk is determined by exposure and the hazard. The concept of pharmaceutical sustainability has traditionally been formulated as a manufacturing issue: minimize solvents, waste, energy and hazardous reagents but maintain quality and yield. These objectives are crucial but not what makes the end API persistent, bioaccumulative or toxic to non-target organisms. On the other hand, a waste-intensive synthesis cannot be justified by a favorable environmental fate.

Benign-by-design and greener-drug frameworks therefore extend analysis from the reaction vessel to the pharmaceutical life cycle [3-7].

Figure 1 summarizes this logic. The pharmaceutical life cycle continues after administration and excretion through transport, transformation, partitioning, exposure and ecological effects. Because structural and economic lock-in increases during development, the greatest design opportunity lies upstream. This review therefore emphasizes early prevention while retaining downstream environmental risk assessment as a distinct discipline [3-5].

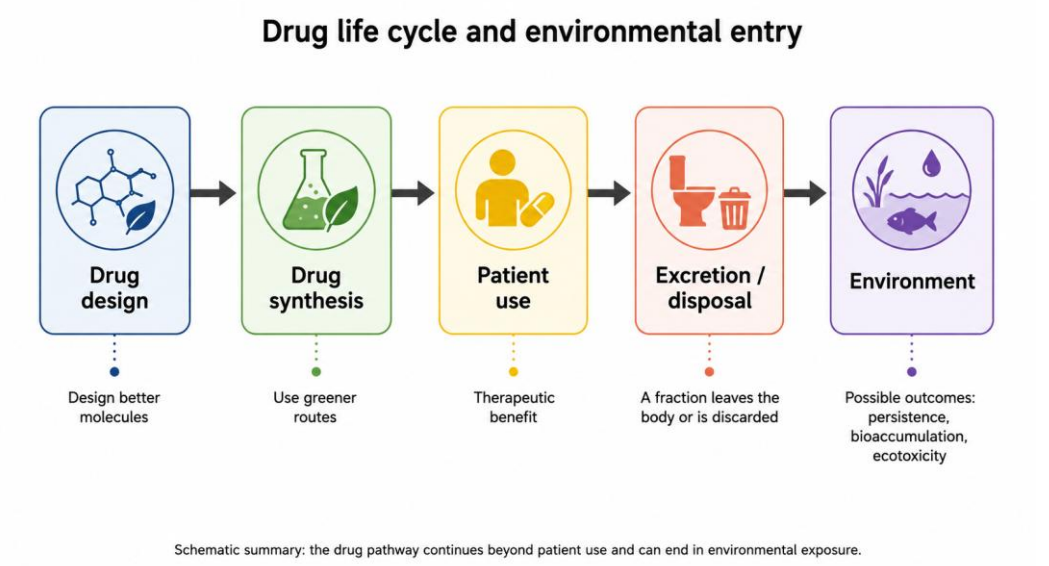

Figure 1. Simplified pharmaceutical life cycle and the main route to environmental exposure. Conceptually adapted from Refs. [1-17]. The figure was redrawn for this review in a simplified schematic format; no published figure was reproduced.

This review does not rename established disciplines or imply that every sustainability endpoint should be optimized from hit discovery. It connects medicinal-chemistry optimization, human ADMET, process burden, environmental fate, ecotoxicity, biodegradability, regulation and AI-enabled decision support, asking when each evidence type becomes strong enough to change a pharmaceutical decision [4-7]. Therapeutic efficacy and patient safety remain non-negotiable; sustainability becomes discriminating among clinically credible alternatives.

Terminology: 'Green synthesis' denotes route- and process-level reduction of material, energy and hazard burdens; 'benign-by-design' denotes deliberate molecular design or redesign to improve post-use environmental behavior while preserving function; and Safe and Sustainable by Design (SSbD) denotes the broader European life-cycle framework for chemicals and materials. 'Green-by-Design pharmaceutical' is used here as an organizing label, not a regulatory designation. Commission Recommendation (EU) 2026/510 revised the voluntary SSbD framework without replacing sector-specific medicinal-product requirements [6,8,18,19].

Scope: The evidence base is dominated by small-molecule human pharmaceuticals, reflecting the literature identified for medicinal chemistry, process sustainability, environmental modeling and human-medicine ERA. The proposed workflow should not be extrapolated automatically to biologics, vaccines, veterinary medicines or non-EU systems. Antimicrobial-resistance-specific assessment,

mixture toxicology and full healthcare-system carbon accounting are important adjacent topics but are not reviewed comprehensively.

Materials and Method

Narrative literature review has been carried out based on literature searches using PubMed and relevant scientific databases and publishers such as ACS Publications, Royal Society of Chemistry, ScienceDirect, Springer Nature, and Wiley Online Library. The search has concentrated mainly on the recent literature which has been published between 2024 and August 2026, and other older literature has been included only when it introduced the fundamental concepts or methodology for green pharmaceutical development. The keywords and the combination of terms used included green pharmaceutical development, sustainable drug discovery, human ADMET, environmental fate, biodegradability, bioaccumulation, ecotoxicity, green chemistry, artificial intelligence, machine learning, and Safe and Sustainable by Design. Appropriate peer-reviewed articles, regulatory documents, and international guidelines by organizations such as EMA, European Commission, and OECD have been selected and critically synthesized based on their relevance in the incorporation of therapeutic efficacy, human safety, process sustainability, and environmental protection. The review has been performed as a narrative synthesis.

Evidence Acquisition

This article is a structured critical narrative review, not a PRISMA systematic review. Searches were updated through 30 August 2026. PubMed was used to verify biomedical and pharmaceutical literature, with targeted title, DOI and topic searches across ACS, RSC, Elsevier, Springer and Wiley platforms. Regulatory and policy statements were checked against official EMA, EUR-Lex, the 2026 European Commission SSbD Recommendation, OECD test-guideline sources and the PREMIER Digital Assessment System [15,16,19-25].

The primary evidence window was 2024-August 2026 because greener medicinal chemistry, environmental prediction and AI-supported optimization are evolving rapidly. Earlier studies were retained when foundational, when they established a widely used metric or framework, or when they demonstrated redesign of an API for improved environmental degradation [8,26,27]. Recency alone was not treated as evidence strength; original studies with external validation or experimental endpoints were weighted above perspectives or purely conceptual frameworks.

Search concepts covered green chemistry and pharmaceutical synthesis; sustainable or benign-by-design medicinal chemistry; environmental fate, PBT, ecotoxicity and biodegradability; life-cycle and process metrics; AI/ML, interpretable QSAR and multi-objective optimization; and environmental risk assessment. Sources were retained when they informed at least one prespecified decision domain: molecular design, human ADMET, route/process selection, environmental fate or effects, regulatory assessment, AI-supported prioritization or implementation. Low-relevance commentary and unverifiable citations were excluded as evidentiary anchors.

Search transparency: Searches were iterative and topic-directed rather than exhaustive database sweeps; database hit counts, duplicate-removal statistics, dual-reviewer agreement and a PRISMA flow are therefore not reported. No single risk-of-bias instrument was appropriate for the heterogeneous corpus of regulatory documents, experiments, modeling studies, reviews and perspectives. Quantitative claims preferentially used original studies, regulatory claims used current primary official documents, and model outputs were interpreted with external validation, endpoint definition and applicability domain where available.

Evidence was synthesized by decision point rather than chronology, separating established practices from emerging capabilities. The analysis thus differentiates between established evidence, promising yet context-specific evidence, and predictions that are not yet reliable enough to be used to make stand-alone decisions.

Results

1. Green chemistry in pharmaceutical development: beyond yield

Green chemistry has been simplified to mean less waste and safer chemistry, but the scope of its operations is prevention, atom economy, safer substances and solvents, energy efficiency, catalysis, renewable inputs where possible, and design to degrade [26]. In pharmaceutical research and development, these principles are transformed into the number of steps, solvent and reagent load, the use of protecting groups, catalyst substitutions, purification requirement and the local burden shift. [27,28].

Yield alone is therefore an inadequate sustainability descriptor. A high-yielding reaction may still require large solvent volumes, reagent excess, repeated chromatography or energy-intensive work-up. PMI and E-factor expose material burden, whereas LCA captures impacts that mass-based metrics can miss. These metrics answer different questions and should be interpreted as complementary, not interchangeable [29-31].

Table 1. Core green chemistry metrics used in pharmaceutical process evaluation**.**

Summarized from Refs. [26-34*].*

Metric	What it measures	Why it matters
Atom economy	Desired-product molecular mass / total molecular mass of stoichiometric reactants	Shows the intrinsic material efficiency of the reaction design.
E-factor	Mass of waste / mass of product	Useful for comparing waste intensity between routes or processes.
Process mass intensity (PMI)	Total mass of materials used / mass of product	Captures solvents, reagents, water and auxiliaries; widely used in pharmaceutical process work.
Reaction mass efficiency (RME)	Practical material efficiency incorporating stoichiometry and yield	Helps distinguish routes with similar yields but different reagent burdens.
Energy demand	Heat, cooling and electricity required by the process	Prevents a material-efficient route from being labelled “green” if it carries a large utility burden.
Life-cycle assessment (LCA)	Impacts across upstream inputs, manufacturing and downstream stages	Adds context that simple mass-based metrics cannot capture on their own.

Solvents often dominate the material footprint of medicinal-chemistry campaigns. An ACS Green Chemistry Institute Pharmaceutical Roundtable analysis of more than 400,000 medicinal-chemistry reactions found that over 40% of profiled reactions used undesirable solvents [32]. Repetition at discovery scale can therefore accumulate across portfolios and become embedded before process development begins.

The toolbox is expanding. Continuous flow can improve heat and mass transfer, containment, safety and process control, while biocatalysis can provide high selectivity under mild conditions when technically and economically appropriate [33,34]. At manufacturing scale, the ACS GCIPR perspective treats sustainability as interacting levers - material efficiency, solvents, energy, supply chains and life-cycle impacts - rather than a single-number optimization problem [29].

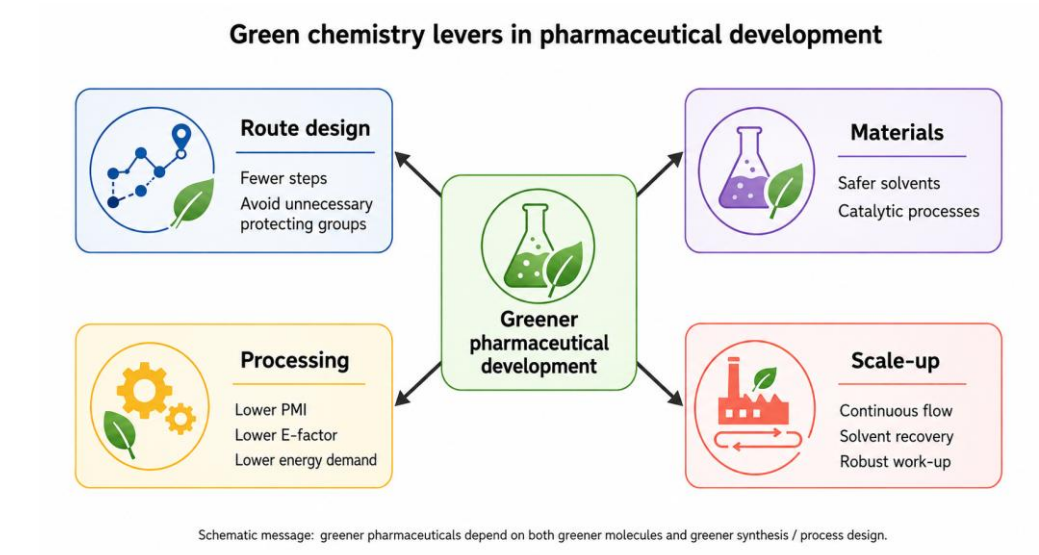

Figure 2. Green chemistry levers across pharmaceutical synthesis and process development. Synthesized from Refs. [26-34]. The diagram was redrawn for this review in a simplified schematic format.

2. From human ADMET to environmental endpoints

The nature of medicinal chemistry is multi-objective: potency should be accompanied by selectivity, solubility, permeability, exposure, clearance, metabolic stability, safety and developability. This offers a connection useful to the environmental thought since certain molecular characteristics affect not only human disposition but also post-use behavior. The analogy should be confined: human ADMET and environmental fate/effects are associated with other matrices, species, exposure periods and endpoints [4,5,8-13].

Figure 3 conceptually bridges with the terms of human ADMET to environmental assessment, not a regulatory or a term in the place of environmental risk assessment. Following excretion, the applicable questions become persistence, mobility, transformation, bioaccumulation, ecological impacts and exposure. Hypotheses can be identified by medicinal-chemistry intuition but regulatory interpretation is in need of environmental evidence standards [4,12,13,15].

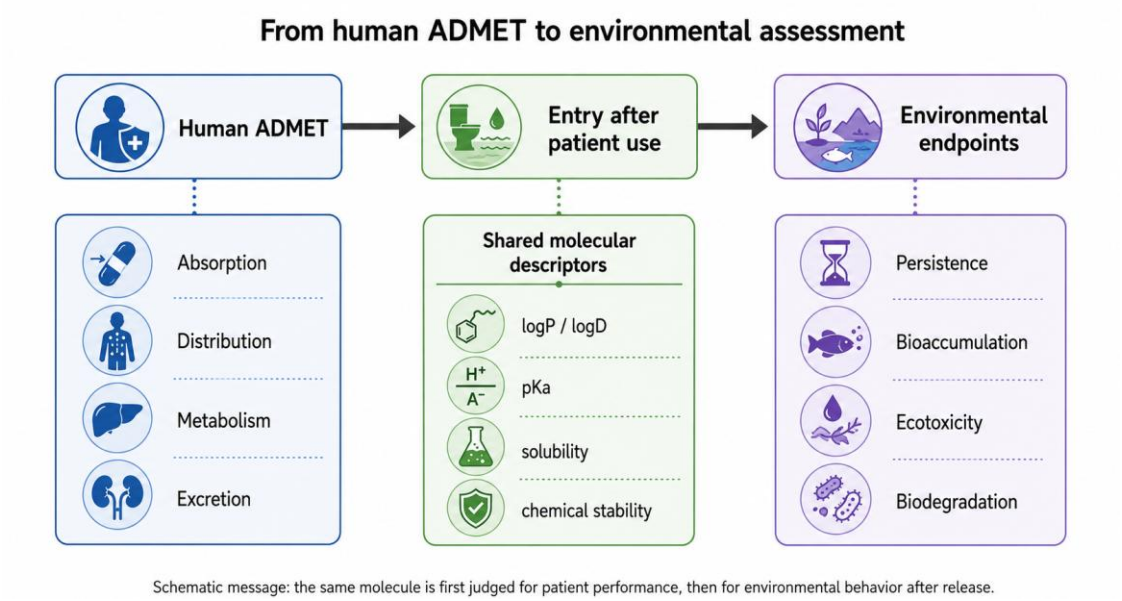

Figure 3. A conceptual bridge between medicinal chemist and environmental assessment: human ADMET to environmental assessment.

Conceptually adapted from Refs. [4,5,8-15]. The figure was redrawn for this review in a simplified schematic format. The term environmental ADMET is not employed as a regulatory term in this context; the diagram merely connects well-known medicinal-chemistry thought to environmental endpoints.

Lipophilicity is used to show why one-directional rules are unsound. Increased lipophilicity can enhance permeability or targeting but also target sorption or partitioning into biota; ionization, metabolism, molecular size and matrix can alter that correlation. Similarly, chemical stability can be conducive to formulation or exposure, but lead to persistence in situations of slow abiotic and biotic transformation. The latter are reasons to reveal trade-offs between otherwise plausible candidates, not to rule out a property in solitude [4,8,11,12].

Table 2 summarizes descriptors that can generate early cross-domain hypotheses. None is a stand-alone environmental decision rule: behavior emerges from structure, speciation, transformation, sorption, exposure, test design and organism context. An early molecular flag should therefore trigger stronger evidence, not an automatic 'green' or 'non-green' classification [8-14].

Table 2. Medicinal chemistry descriptors and possible environmental implications.

Based on Refs. [4,5,8-14]. These relationships are context-dependent and are not direct regulatory thr*esholds.*

Descriptor / property	Human relevance	Possible environmental relevance
logP / logD	Membrane permeability, tissue distribution and exposure	May influence sorption and partitioning into biota; interpretation depends on ionization, metabolism and molecular size.
pKa / ionization	Absorption, solubility, permeability and target exposure	Controls environmental speciation and can alter mobility, sorption and bioavailability across pH conditions.
Aqueous solubility	Formulation, dissolution and systemic exposure	Influences aqueous transport and measurable exposure, but low solubility can shift burden toward particles, sediment or biota.
Chemical / metabolic stability	Shelf life, exposure and duration of pharmacological action	Slow transformation can contribute to persistence, but metabolic stability in humans is not equivalent to environmental persistence.
Biodegradation susceptibility	Rarely a routine medicinal-chemistry optimization endpoint	Central to benign-by-design strategies; predictions should be treated as screening evidence until supported by validated biodegradation data.

3. Persistence, bioaccumulation, ecotoxicity and transformation products

Ecological harm is not the same as environmental detection. Risk is exposure plus inherent hazard: persistence may extend exposure, bioaccumulation may augment internal dose and ecotoxicity is defined as effects in specified biological situations. PBT terminology can be used to screen and prioritize but not fully characterize the risk without exposure information [11-13,15]. Recent computational research reinforces early screening but demonstrates why performance is necessary to be explicit. Evangelista et al. were able to use message-passing neural networks to predict PBT characteristics of pharmaceuticals [11]. The ROC-AUC values were reported as 94.60% bioconcentration and 96.06% ecotoxicity in the 2026 G.AI.A study, benchmarking screening to reported values with internal and external validation [12]. These findings are endpoint-, dataset- and chemical-space-specific, so the applicability domain and external validation are necessary. The importance of transformation products is that the disappearance of parents alone cannot create

environmental safety. Degradation can produce products that are stable, diffusive or bioactive. It is demonstrated in a study of sulfonamide redesign that structural alterations can enhance desired pathways of transformation but without necessarily ensuring easy biodegradability [10]. Designing to degrade is thus a falsifiable hypothesis to be proven product-consciously, rather than qualitatively. Boucetta et al. took a review of the intersection of QSAR/ML prediction with analytical methods in the identification of pharmaceuticals and transformation products in real matrices [13]. The methodological strength is complementary: models reduce chemical space to testable hypotheses, whereas analytical chemistry and ecotoxicology help to find out whether the hypotheses can be true in real-life situations.

4. Biodegradability-by-design: an attractive goal with a difficult trade-off

Biodegradability-by-design is fundamentally easy conceptually and chemically challenging: maintain potency, selectivity, exposure, stability and shelf life and transform into post-use non-toxic products. Puhlmann et al. defined this as a benign-by-design issue [8]. The main question is thus whether a structural space that is clinically acceptable has alternatives that have more significantly better environmental mineralization. It is a real tension since modifications in lipophilicity, ionization, metabolic stability and steric accessibility may enhance therapeutic characteristics and modify environmental transformation or partitioning in the reverse way [4,8-10].

A defensible Green-by-Design strategy therefore seeks Pareto improvements - or transparent trade-offs - rather than a universal biodegradability threshold.

Computational biodegradability prediction is best used for early triage. In 2026, Groth et al. evaluated nine freely available models against 50 pharmaceuticals/APIs with experimentally validated OECD 301D data; all fell below the 80% performance benchmark used by the authors, and models were generally better at identifying non-biodegradable compounds than confirming ready biodegradability [14]. Thus, current tools can support prioritization or deselection, but a favorable prediction is not evidence of environmental safety.

Testing should therefore escalate with decision consequence: low-cost prediction early, standardized or fit-for-purpose environmental experiments for shortlisted candidates, and regulatory-grade evidence when a claim or development decision depends on it [14,15,21-25]. Alternative and animal-reducing ecotoxicology strategies are valuable but remain endpoint-specific and require appropriate validation [35].

5. AI and automation: useful when they expose trade-offs

AI is changing reaction planning, property prediction and molecular optimization, but sustainability improves only when sustainability-relevant variables enter the objective function. Optimizing solely for potency, yield or synthetic accessibility can still favor undesirable solvents or environmental profiles. The key question is therefore which objectives, constraints, uncertainty estimates and validation standards govern the recommendation [18,36-38].

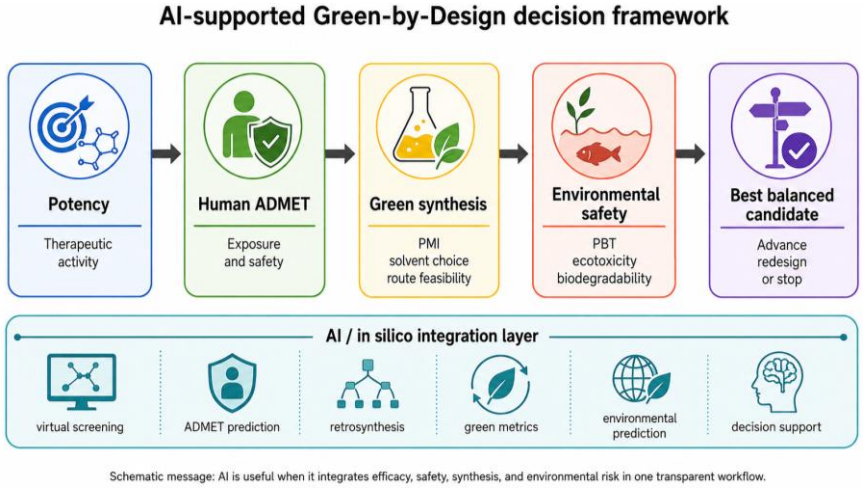

Figure 4. AI-supported multi-objective Green-by-Design decision framework.

Conceptually adapted from Refs. [11-14,18,20,35-41]. This review has re-sketched the framework in a simplified schematic form and highlights visible trade-offs, as opposed to a single opaque score of green. Recent surveys indicate that already built-in AI-sustainability concepts are present in the field. Gaikwad assessed AI and quantum-chemical methods to greener synthesis [36], Gangwal and Lavecchia assessed LLMs, automation and sustainability metrics in medicinal chemistry [37], and Lopez-Lopez et al. suggested an AI-enabled benign-by-design ligand framework that combines efficacy, safety and environmental sustainability [18]. The value of the current review is thus functional: the connection between molecular design and process measures, environmental evidence, regulatory escalation and stage-specific decisions of R&D. The worth of measurable multi-objective optimization is demonstrated in original studies. Wang et al. integrated Bayesian optimization, real-time spectroscopy and semiautomated execution of an apixaban intermediate at a 27% reduction in reagent cost, 31% reduction in electricity consumption, 54% reduction in PMI and 98% reduction in side products [39]. The methodological aspect is that the algorithm was optimal at a vector of results, and not just at a yield. On the molecular level, G.AI.A and deep-learning PBT research indicate a concurrent approach: evaluate the performance of therapeutics, human ADMET, synthetic burden and environmental forecasting and maintain model uncertainty and applicability domain [11-13]. To support decision making, Pareto-style comparison or transparent endpoint dashboards would be better than a single composite green score due to the ability to reveal the accepted trade-off as well as the least effective evidence. A 2026 antibacterial study used a combined design-of-experiments synthesis optimization, biological testing, early drug-like profiling and predicted biodegradability [40]. A 2026 study applied interpretable QSAR, q-RASAR and ML to high-throughput acute oral toxicity screening, demonstrating how computational triage can help to avoid redundant synthesis and animal study [38]. These illustrations help to justify integration as a workflow principle, but not as an industrial standard that has proven its universality. The evidence hierarchy is also indicated by representative studies: apixaban optimization has gave quantified process-level evidence [39]; sulfonamide redesign demonstrates that transformation-product evidence can be used to guide molecular redesign with no guarantee of environmental safety [10]; G.AI.A has provided strong endpoint-specific prediction but not environmental safety certification [12]; and the oxyprenyl-chalcone study has integrated synthesis, activity, drug-like profiling and predicted biodegradability but not performed with regulatory-grade environmental validation [40]. Of the sources found during this review, none of them covers prospectively therapeutic efficacy, human ADMET, process metrics, environmental fate/effects and regulatory validation end to end. This disparity drives the stage-gated architecture in this paper.

6. What is already covered, and where the literature is still fragmented

The literature now includes substantial overlap among green synthesis, environmental design and AI. For Table 3, comparator publications were selected because they directly overlap with at least two core domains of this review and are sufficiently recent to test its claimed contribution. They are compared on four dimensions: scope, decision level, validation emphasis and implementation pathway.

Table 3. Selected recent literature that frames the novelty of this review.

All entries were verified against publisher, PubMed or official sources.

Study	Year	Main contribution	Main limitation / gap
Vidaurre et al. [4]	2024	Links pharmaceutical R&D parameters with environmental impact drivers.	Strong design perspective; less emphasis on AI-enabled synthesis and stage-gated validation.
Puhlmann et al. [6]	2024	Applies Safe and Sustainable by Design concepts to pharmaceuticals.	Framework-focused rather than a full medicinal-chemistry-to-regulatory

		workflow.	
Bertram et al. [9]	2025	Defines the practical challenge of environmentally biodegradable drugs.	Short opinion article; limited methodological and implementation depth.
Tsoukas et al. [12]	2026	Demonstrates ML prediction of bioconcentration and ecotoxicity, including metabolites.	Endpoint-specific original study rather than an integrated pharmaceutical workflow.
Gaikwad [36]	2026	Reviews AI and quantum chemistry in green organic synthesis for drug discovery.	Environmental fate after patient use is not the central focus.
Boucetta et al. [13]	2026	Bridges in silico prediction with analytical environmental tools.	Does not treat process sustainability and medicinal-chemistry decisions in equal depth.
López-López et al. [18]	2026	Proposes AI-enabled benign-by-design ligand optimization integrating efficacy, safety and sustainability.	Strong molecular-design framework; less emphasis on pharmaceutical process metrics, regulatory escalation and stage-gated environmental evidence.
Shalin et al. [42]	2026	Identifies systemic lock-ins that prevent early integration of environmental safety and sustainability in drug development.	Implementation-focused perspective rather than a molecular/process evidence synthesis.
Present review	2026	Integrates human ADMET, molecular design, process metrics, environmental fate/effects, validation, regulation and AI by R&D decision stage.	Framework remains a critical synthesis; several environmental endpoints still lack broad prospective industrial validation.

The novelty is not that green synthesis, ERA, ADMET prediction, benign-by-design or AI-enabled sustainability are individually new. A 2026 review already places AI-enabled multi-objective ligand design within an environmental sustainability context [18]. The present contribution is narrower: a stage-gated decision architecture connecting molecular optimization, process burden, environmental hazard and exposure evidence, experimental escalation, regulation and implementation. The unit of integration is the R&D decision, not a new acronym or opaque sustainability score [4-7,10-14,18,35-39,42].

7. Regulatory and implementation landscape

Environmental risk assessment is now embedded in medicinal-product regulation. EMA's environmental risk assessment guideline, Revision 1, has been effective since 1 September 2024 and retains a phase-based ERA in which exposure and effect information determine escalation [15]. Its Phase I surface-water action limit of 0.01 microgram/L is a screening trigger, not a universal 'safe' or 'green' concentration, and is not applicable in all cases. Molecular-design frameworks should therefore not repurpose it as a medicinal-chemistry cutoff.

Commission Recommendation (EU) 2026/510, adopted on 6 March 2026, revised the European Safe and Sustainable by Design framework for chemicals and materials [19]. SSbD is a voluntary anticipatory framework intended to expose safety, sustainability, functionality and life-cycle trade-

offs during innovation; it does not create or alter Union legal obligations. In pharmaceutical R&D it complements, rather than substitutes for, medicine-specific ERA.

Directive (EU) 2024/3019 adds a different pressure by requiring Member States to establish extended producer responsibility for listed products by 31 December 2028, with producers covering at least 80% of specified quaternary-treatment and micropollutant-monitoring costs [16]. Although a wastewater policy rather than a drug-design guideline, it makes the downstream economic consequences of persistent micropollutants more visible and strengthens the case for upstream prevention.

Implementation remains difficult. A 2025 scoping review identified investment cost, regulatory complexity and cross-stakeholder coordination as recurring barriers [17]. Shalin et al. later described two systemic 'lock-ins': environmental expertise often arrives after the most modifiable stages of molecular design, and incentives favor new products over environmentally motivated redesign [42]. These findings support stage-specific integration rather than a generic sustainability checklist.

Table 4. Regulatory and implementation context relevant to greener pharmaceuticals.

Sources: Refs. [6,7,15-17,20,42].

Domain	Current position	Why it matters for drug development
EMA environmental risk assessment	Revision 1 has been effective since 1 September 2024. Phase I uses predicted exposure as a screening step; the 0.01 microgram/L surface-water action limit is not a universal safety threshold and is not applicable in all cases.	Creates a formal medicinal-product ERA pathway and prevents early design frameworks from being confused with regulatory proof of environmental safety.
EU urban wastewater directive	Directive (EU) 2024/3019 requires EPR measures by 31 December 2028; producers cover at least 80% of specified quaternary-treatment and monitoring costs.	Creates a downstream economic signal that strengthens the value of upstream prevention, without itself becoming a molecular-design rule.
Safe and Sustainable by Design	Commission Recommendation (EU) 2026/510 revised the European SSbD framework in March 2026. It is voluntary and does not replace legal or medicine-specific requirements.	Provides a life-cycle decision framework for anticipatory design, but pharmaceutical endpoints and EMA ERA obligations must remain distinct and interpretable.
PREMIER Digital Assessment System	Database version 0.10.1 provides verified experimental environmental data for APIs and calculated physicochemical information; the ERA Tool remains under development.	Demonstrates the importance of shared, quality-controlled data while avoiding the implication that the assessment module is already a mature regulatory tool.
Implementation evidence	Scoping and systems analyses identify cost, coordination, resource-timing and incentive lock-ins [17,42].	A technically strong framework will fail if expertise arrives after structural decisions are effectively locked.

Another bottleneck is data infrastructure. As of v0.10.1 (5 June 2026), the PREMIER Digital Assessment System gives validated experimental environmental values of APIs on top of calculated physicochemical data and the ERA module is still in development [20]. Since the environmental models rely on curated endpoints, domains of applicability and reproducible assay context

[11,12,14,20], data harmonization and provenance transparency are facilitating infrastructure, as opposed to secondary informatics information.

8. A practical Green-by-Design workflow for pharmaceutical R&D

The evidence favors a staged workflow rather than a uniform environmental gate. At hit identification, low-cost computational flags are appropriate; during lead optimization, synthetic burden and preliminary environmental profiles can discriminate among therapeutically comparable candidates. By pre-development, decision-relevant claims require targeted experiments, while life-cycle review should integrate process metrics, environmental risk evidence and LCA where relevant [4,5,8-14,18,21-25,38,42].

Table 5 applies a conservative escalation principle: use the least expensive evidence capable of changing the current decision, then strengthen evidence as the cost of error rises. This is especially important for biodegradability, where a favorable in silico result is weaker than a negative persistence flag [14]. Early prediction prioritizes; later testing confirms, characterizes and supports regulatory defensibility.

Table 5. A staged Green-by-Design workflow for pharmaceutical R&D.
Synthesis of the evidence in Refs. [4-18,20-25,29-31,37-42].

R&D stage	Main question	Evidence used	Decision
Hit identification	Can obvious synthetic or environmental liabilities be avoided before chemistry expands?	Structural alerts, route awareness, simple physicochemical and environmental flags with applicability-domain checks.	Advance / redesign / deprioritize
Lead optimization	Among therapeutically credible leads, do sustainability-relevant differences justify reprioritization?	Human ADMET + preliminary PBT/ecotoxicity/biodegradation evidence + synthetic burden + uncertainty.	Prioritized shortlist / targeted test
Route selection	Which practical route reduces material, solvent, hazard and energy burden without shifting impacts elsewhere?	PMI, E-factor, solvent guidance, process alternatives; LCA screening where justified.	Preferred route / mitigation plan
Pre-development	Which unresolved environmental question could materially alter candidate value or later ERA?	Targeted standardized/fit-for-purpose biodegradation, transformation-product, bioaccumulation or ecotoxicity testing.	Go / mitigate / reassess
Lifecycle review	Do scaled manufacturing, use and post-use evidence support a coherent patient-and-planet case?	Integrated process metrics, LCA where decision-relevant, exposure/effects evidence and ERA documentation.	Documented benefit-risk-sustainability rationale

Therapeutic primacy must remain explicit. Rapid degradation cannot rescue an ineffective medicine, and a favorable environmental profile cannot justify an unsafe therapy. The realistic objective is patient-and-planet optimization: first satisfy therapeutic requirements, then use credible process and environmental differences to discriminate among viable alternatives [41,43-45].

Table 6. Prediction-to-validation ladder for environmental evidence in Green-by-Design pharmaceutical R&D.

Synthesized from Refs. [10-15,21-25].

Question	Early computational role	Experimental escalation	Decision meaning
Persistence / biodegradability	Flag likely persistent structures; compare candidates within model applicability domain.	OECD TG 301 or fit-for-purpose biodegradation testing; characterize transformation products when relevant.	Negative flags can support early deprioritization; positive predictions require confirmation before environmental claims.
Bioaccumulation	Predict BCF/BMF tendency and identify structural drivers.	OECD TG 305 or justified alternative evidence when bioaccumulation is decision-critical.	Use as a weight-of-evidence endpoint, not a direct surrogate for clinical lipophilicity.
Ecotoxicity	Prioritize compounds / endpoints and estimate relative concern.	Use standardized algae, invertebrate and fish tests appropriate to the scientific question; for regulatory ERA, follow the phase-specific EMA test requirements rather than treating any single acute test as sufficient.	Escalate testing when predicted hazard could alter candidate ranking or ERA. Screening assays and acute tests are not automatically regulatory-complete evidence.
Transformation products	Predict plausible metabolites/degradates and prioritize analytical targets.	Analytical identification plus persistence/effect testing of relevant products.	Parent disappearance is insufficient if products retain persistence or biological activity.
Integrated environmental risk	Combine fate/effect flags with exposure assumptions for screening.	Regulatory ERA evidence and exposure-effect characterization at later stages.	Risk requires both hazard and exposure; screening classifications must not be presented as complete risk estimates.

Table 6 is an evidence-escalation guide, not a regulatory checklist. The OECD methods are examples of standardized tests; marketing-application studies must follow applicable EMA phase-specific requirements and substance-specific considerations [15,21-25].

Table 7. Minimum controls for decision-grade AI support in Green-by-Design R&D.

Proposed by the present review, informed by Refs. [11-14,18,20,38].

Control	Minimum evidence to retain	Failure prevented
Endpoint definition	State exactly what is predicted, how the endpoint was measured or labelled, and whether it is a	Prevents a high-performing surrogate model from being interpreted as proof of a

	regulatory endpoint, proxy or screening construct.	different environmental property.
Data provenance and independence	Retain data origin, curation rules and train/validation/test separation; use an independent external set when feasible.	Reduces leakage, duplicated chemistry and optimistic internal performance.
Applicability domain	Report whether the candidate lies inside the chemical and endpoint domain represented by the training data.	Prevents confident extrapolation to chemistry the model has not learned.
Uncertainty	Expose confidence, model disagreement or other uncertainty information rather than returning only a point prediction.	Distinguishes robust ranking from a fragile estimate and identifies where testing has highest value.
Prospective confirmation	Escalate to an appropriate experiment when a prediction could change candidate selection, support an environmental claim or enter ERA.	Prevents computational triage from being mistaken for validated environmental evidence.
Auditability	Retain model/version, inputs, key assumptions and the reason the output changed a decision.	Allows reproduction, internal challenge and later reinterpretation as models or regulatory expectations evolve.

'Decision-grade' is used here as a practical review term, not a regulatory classification; required evidence should increase with the consequence of the decision.

9. Current gaps and research priorities

The first one is a data asymmetry. The decades of standard pharmacology and toxicology are an advantage of human ADMET, and the environment data sets are smaller and diverse. Spilsbury et al. found 1,763 APIs approved in the European Economic Area, of which only 27 (1.5%) had enough public exposure and ecotoxicity information for risk assessment, and 1,201 (68%) lacked any public monitoring or ecotoxicity data [46]. The endpoint definition, provenance, applicability domain and uncertainty ascertains whether a prediction is decision-grade or not [10-14,20,46]. The second dissonance is objective conflict. Exposure- or target-engaging medicinal-chemistry properties may act in opposition to environmental degradability but series- and mechanism-dependent. Study has to find true Pareto improvements, design around solvable trade-offs and find alterations that only redistribute load among destinations [4,8-10]. The third is the metric fragmentation gap. PMI, E-factor, solvent guides, energy demand, LCA, PBT models, biodegradation tests and ecotoxicity tests characterize various dimensions. Their conflict can be instructive: mass- and energy-based measures of the processes are correlated weakly to moderately with various life-cycle impact measures [31]. Multidimensional evidence and uncertainty should thus be maintained by digital tools and not reduce to a single universal score. The fourth gap is implementation and timing. It does not matter to a great extent when environmental knowledge is brought in when medicinal-chemistry decisions are in. Useful systems need to respond to stage-specific questions, reveal uncertainty, integrate R&D data infrastructure and provide ownership of follow-up evidence. Incentives and timing of the organization can be as restrictive as model performance [17,42].

Discussion

Sustainability in pharmaceuticals is shifting towards a process-only paradigm to coupled molecular and process design, although evidence maturity is still uneven. The industrially rooted process metrics and quantified optimization [27-34,39]; the environmental ML facilitates endpoint-specific prioritization in discrete areas [11-14], but the biodegradability prediction is less robust [14]. Molecular redesign: In the chosen series [8,10,40], but out of the identified sources in this review, no prospective program demonstrates therapeutic performance, human ADMET, process sustainability, environmental fate/effects and regulatory readiness end to end. This maturity scale promotes a stage-based and not prescriptive model. There is also a life-cycle view of why the process and molecular evidence cannot be substituted. The manufacturing decisions dictate material and energy and hazard load, molecular structure affects persistence, transformation, bioaccumulation and ecotoxicity. A low-PMI route does not create a benign API and a degradable API does not warrant a risky procedure. Integration must then be at the decision level whilst maintaining the separation between evidence domains [6-9,29-31]. The concept of human ADMET is a convenient conceptual bridge since medicinal chemists are already dealing with constrained multi-objective optimization, whereas environmental endpoints entail other organisms, exposures and evidence standards. The opportunity in practice is to employ sufficiently credible environmental evidence to prioritize therapeutically plausible options, without treating environmental science to be another column of human ADMET [4,5,10-14]. The decision-making of environment is not at the point where AI can be blindly applied to rank complex options. There is high performance of chosen PBT-related and ecotoxicity models, but the biodegradability is less reliable [11-14]. Viable use thus demands extraneous validation, applicability-domain testing, uncertain-yielding products and future validation. AI must reduce the search space and reveal trade-offs, as opposed to certifying that a molecule is green. Incentives are also being transformed by regulation. The formalisation of environmental assessment is carried out by EMA ERA Revision 1, and the exposure of part of the downstream cost of micropollutant removal to the producers is carried out by the recast EU wastewater directive [15,16]. Systems analyses indicate that the timing of expertise and redesign incentives limits environmental integration [42]. Regulatory pressure is thus best applied when converted to actionable early-stage criteria as opposed to being left as late compliance. There are limitations of this review. It is a formal narrative synthesis of critical analysis as opposed to a comprehensive systematic review; focused, iterative searching might have missed pertinent studies and publication/reporting bias was not quantified formally. The heterogeneous combination of experiments, modeling studies, reviews, perspectives and regulatory documents could not have been addressed by any pooled meta-analysis or general risk-of-bias tool. Regulatory analysis is EU-focused and the empirical environmental literature is biased towards aquatic endpoints, thus the conclusions cannot be automatically generalized to other jurisdictions, compartments, biologics, veterinary medicines, antimicrobial-resistance-specific assessment effects or mixture effects. A number of 2026 ideas, especially future multi-objective molecular design using environmental endpoints, are still largely backed by only proof-of-concept evidence. The framework is to be understood as an evidence based decision architecture and research agenda rather than a standards of regulation.

Conclusion

Green chemistry in pharmacy is shifting to a question of manufacturing-only, to a coupled-design and life-cycle decision-making. The manufacturing burden can already be decreased by using safer solvents, catalysis, biocatalysis, continuous processing, PMI, E-factor and LCA [27-34]. The less developed challenge is to implement environmental fate and effects at an early stage to impact on molecular choice without affecting therapeutic performance [3-14,18]. To help in this transition, AI can rank the chemical space, identify PBT-like behavior, and suggest experiments on the environment, and suggest paths and optimization processes. Its worth is pegged on open endpoints, domains of applicability, external verification and doubt. Biodegradability is the most obvious where prediction should be used in testing as opposed to substituting it [10-14,18,35-39]. Patient-and-planet-centered is the most plausible model. Entry conditions are clinical efficacy and patient safety; of the

viable therapeutic options, sustainability should prefer candidates and routes that do not bear unnecessary material load, hazard and long-lived environmental impact, as evidence accumulates and reversing the decision grows more difficult. This is an action-oriented and scientifically cautious stage-gated approach [18,20,38,41-45].

Findings

1. Green-by-Design needs to incorporate molecular environmental behavior with process efficiency at the R&D decision level, not equate sustainability with green synthesis alone.
2. The conceptual bridge between human ADMET and environmental assessment needs different endpoints, species, exposure assumptions and evidence standards.
3. AI/ML can give precedence to the PBT-related, bioaccumulation and ecotoxicity issues, and the positive biodegradability forecasts still need to be experimentally validated.
4. Multi-objective optimization is most justifiable in instances where trade-offs, area of applicability and uncertainty is not dwarfed into a single sustainability score. Integrated AI-sustainability frameworks are already present so the specific contribution is functioning: a stage-gated connection between molecular design, process metrics, validation, regulation and R&D decisions..

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