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Beyond Traditional Chemistry: Pioneering Green Synthesis in Pharmaceuticals

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Authors' contributions

This work was carried out in collaboration among all authors. Author AK contributed to the conceptualization and data collection for the study. Author FG was responsible for data analysis and drafting the initial manuscript. Author SN provided supervision, critical revisions, and contributed to the study design. Author VP led the project administration, coordinated the research efforts, and finalized the manuscript for submission. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Green chemistry principles are increasingly essential for sustainable pharmaceutical synthesis, aiming to reduce environmental impact while maintaining efficiency and product quality. This review systematically examines recent advances in green synthetic strategies, including solvent alternatives, catalytic approaches (biocatalysis, organocatalysis, transition metal catalysis), and

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process intensification techniques such as flow chemistry. Data were collected from peer-reviewed journals indexed in Scopus and PubMed over the past decade, focusing on innovative methodologies, industrial applications, and sustainability assessment tools.
The results highlight significant progress in adopting green solvents like water and supercritical CO_2, which lower toxicity and waste. Catalysis methods, especially biocatalysis and organocatalysis, provide high selectivity and milder reaction conditions, reducing hazardous by-products. Flow chemistry enables continuous processing with enhanced safety and efficiency. Moreover, sustainability metrics such as atom economy, E-factor, and process mass intensity alongside life cycle assessment (LCA), offer quantitative means to evaluate and optimize environmental performance. Despite these advances, challenges remain in catalyst scalability, regulatory compliance, economic feasibility, and broader industrial implementation. Emerging trends including artificial intelligence- driven route design, enzyme engineering, and circular chemistry hold promise to address these barriers. The integration of green chemistry with digital tools and sustainability metrics facilitates data-driven process development and supports regulatory and corporate sustainability goals.
In conclusion, green chemistry is transforming pharmaceutical manufacturing toward a more sustainable future, balancing ecological responsibility with innovation and efficiency. This review provides comprehensive insights and practical guidance for researchers and industry professionals aiming to advance sustainable pharmaceutical synthesis.

Keywords: Green chemistry; pharmaceutical synthesis; biocatalysis; organocatalysis; flow chemistry; sustainable catalysis; green solvents.

1. INTRODUCTION

The pharmaceutical industry is under increasing pressure to reduce its environmental footprint while maintaining efficiency in drug development. Conventional synthetic routes are often associated with high energy demands, hazardous reagents, and excessive solvent use, all of which contribute to significant ecological and health risks. On average, pharmaceutical processes generate 25 to 100 kg of waste per kilogram of active pharmaceutical ingredient (API) produced far higher than in other chemical sectors (Sheldon, 2007). Additionally, many of these synthetic methods involve multistep reactions with poor atom economy and minimal regard for environmental impact (Tucker, 2006).

Green chemistry offers a transformative approach to chemical design and manufacturing. It is based on 12 core principles that aim to minimize the generation and use of hazardous substances from the outset of a process, rather than treating waste after its formation (Anastas & Warner, 1998). These principles include the use of safer solvents, energy efficiency, renewable feedstocks, catalysis, and inherently safer chemistry for accident prevention (Federsel, 2013). Among the key metrics for evaluating green processes, the *Environmental factor* (E-factor) which is the ratio of waste to product has been widely adopted. While bulk chemical production may have E-factors below 5, pharmaceutical processes often exceed 25, clearly demonstrating the need for more sustainable practices (Constable et al., 2002).

Recent advancements demonstrate that green chemistry is not just a theoretical ideal but a practical necessity in modern pharmaceutical synthesis. For instance, Merck & Co. redesigned the synthesis of sitagliptin, replacing a rhodium-based catalyst with a transaminase enzyme. This modification not only increased yield and reduced cost but also eliminated the need for hazardous reagents and significantly cut down waste generation (Huffman et al., 2019). This case illustrates how integrating biocatalysis a key green chemistry tool into industrial processes can yield both ecological and economic benefits.

Biocatalysis, which uses natural catalysts such as enzymes and microorganisms, has become increasingly prominent due to its specificity, operational simplicity, and alignment with green principles. It allows for reactions to occur under mild conditions (e.g., room temperature and atmospheric pressure), significantly reducing energy input and by-product formation (Pollard & Woodley, 2007). Industrial applications include the synthesis of chiral intermediates for statins, beta-blockers, and antivirals, showcasing the scalability and utility of this approach (Schrittwieser et al., 2018).

Another significant development is the application of continuous flow chemistry, which

offers safer and more efficient processes than traditional batch methods. Flow reactors enable precise control over reaction parameters, faster reactions, and better scalability, all while reducing solvent usage and waste generation (Wegner et al., 2012). These methods also align well with process intensification strategies that are increasingly being adopted across pharmaceutical manufacturing to meet both regulatory and sustainability goals.

In summary, green chemistry approaches are increasingly being integrated into pharmaceutical synthesis to address challenges related to environmental sustainability, process efficiency, and safety. This review explores the evolution and application of green chemistry in pharmaceutical synthesis, including key principles, biocatalysis, catalytic strategies, green solvents, and industry-driven innovations that contribute to cleaner, safer, and more efficient drug development.

2. PRINCIPLES OF GREEN CHEMISTRY AND METRICS

Green chemistry is built on twelve foundational principles that guide the development of environmentally responsible and resource-efficient chemical processes. Introduced by Anastas and Warner in 1998, these principles have become essential in redesigning pharmaceutical synthesis to minimize ecological impact while maintaining product quality and process efficiency (Kar et al., 2022). Key tenets include waste prevention, atom economy, safer solvents and auxiliaries, energy efficiency, renewable feedstocks, and the use of catalysis. In the context of pharmaceuticals, these principles are not only scientifically valid but increasingly vital due to regulatory, economic, and environmental pressures.

Among the most widely used quantitative tools derived from these principles is the E-factor, which measures the mass of waste generated per unit mass of product. Lower E-factors signify cleaner processes, and while bulk chemical industries typically achieve E-factors below 5, pharmaceutical processes often range from 25 to over 100 highlighting the pressing need for greener synthetic alternatives (Vidaurre et al., 2024). Another widely used metric is atom economy, which assesses how efficiently reactants are incorporated into the final product. A high atom economy indicates a streamlined process with minimal generation of side products or waste. In recent years, additional metrics such as process mass intensity (PMI) and life-cycle assessments (LCA) have gained traction for providing a more holistic view of a process's sustainability, extending beyond the chemical reaction to include raw material sourcing, energy usage, and waste treatment (Vidaurre et al., 2024).

The pharmaceutical industry has adopted various green synthetic strategies based on these principles. Solvent-free reactions, or those employing benign alternatives like water, ethanol, and supercritical carbon dioxide, are increasingly common. Additionally, techniques such as multicomponent reactions (MCRs) and one-pot syntheses reduce the need for multiple purification steps, improving both atom economy and overall process efficiency (Kar et al., 2022). Similarly, continuous flow chemistry and process intensification allow for better control of reaction parameters, reduced solvent volumes, and lower energy consumption, making them ideal for scaling up green synthesis methods.

The integration of green chemistry metrics and principles into the design phase of pharmaceutical development is no longer optional it is a strategic imperative. By adopting a “benign by design” approach, pharmaceutical scientists are now beginning to consider environmental impact alongside pharmacological performance when designing new drug candidates (Vidaurre et al., 2024). This shift supports the creation of cleaner, safer, and more sustainable manufacturing routes while meeting global expectations for environmental responsibility.

3. GREEN SYNTHESIS STRATEGIES AND SOLVENT ALTERNATIVES

Green synthesis strategies have gained significant traction in pharmaceutical manufacturing as industries aim to mitigate environmental impact, improve process efficiency, and comply with increasingly stringent regulatory frameworks. At the core of these strategies lies the adoption of greener solvents and innovative reaction conditions that collectively reduce hazardous waste generation and energy consumption.

Table 1. Summary of green chemistry principles and metrics in pharmaceutical synthesis

Principle / Metric	Description	Application in Pharma Synthesis	Benefits
Waste Prevention	Avoiding waste generation rather than treating it afterward	Process redesign to minimize by-products	Reduces environmental impact and disposal costs
Atom Economy	Maximizing incorporation of all materials into the final product	One-pot reactions, MCRs	Enhances material efficiency
Safer Solvents and Auxiliaries	Using non-toxic, biodegradable, or no solvents	Replacement of organic solvents with water, ethanol, or supercritical CO_2	Lowers toxicity and solvent waste
Energy Efficiency	Conducting reactions at ambient temperature and pressure	Microwave-assisted synthesis, flow chemistry	Reduces energy consumption
Renewable Feedstocks	Using materials derived from renewable sources	Biomass-derived starting materials	Promotes sustainability and reduces dependency
Catalysis	Using catalysts instead of stoichiometric reagents	Biocatalysis, metal catalysis	Improves selectivity, reduces waste
Process Intensification	Improving efficiency through continuous flow or in-line monitoring	Continuous manufacturing, PAT implementation	Streamlines processes and reduces variability
E-factor	Ratio of total waste generated to product obtained	Widely used in process evaluation	Quantifies process cleanliness
Atom Economy (Metric)	Percentage of reactants converted to desired product	Applied in route selection	Measures synthesis efficiency
PMI (Process Mass Intensity)	Total mass input per mass of product	Evaluates solvents, reagents, workups	Enables full process comparison
LCA (Life Cycle Assessment)	Assesses environmental impact across entire process life cycle	Incorporates raw material sourcing, energy, and emissions	Guides sustainable decision-making

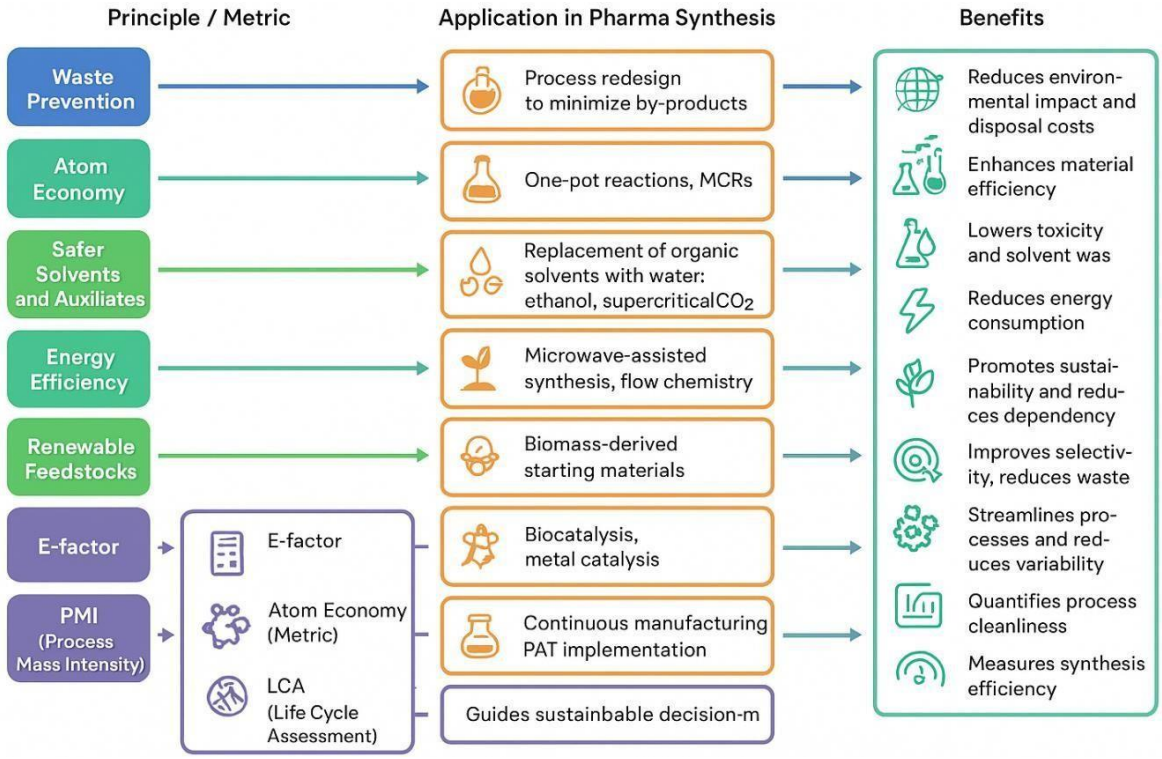

Fig. 1. Green chemistry principles and metrics in pharmaceutical synthesis

Traditional pharmaceutical synthesis often relies heavily on volatile organic solvents such as dichloromethane, benzene, and toluene, which pose serious health risks and environmental concerns. These solvents contribute to significant hazardous waste and volatile organic compound (VOC) emissions, complicating waste management and increasing overall process costs (Clark, 2020). The shift towards greener solvents thus represents a fundamental step in reducing the environmental footprint of drug manufacturing.

Water is considered the most environmentally benign solvent due to its non-toxic, non-flammable nature and abundance. However, its limited solubility for many organic compounds has historically restricted its use. Recent advances in reaction engineering and catalyst design, including micellar catalysis and phase-transfer catalysts, have overcome many solubility challenges, enabling water to act as an effective solvent or co-solvent in a variety of pharmaceutical syntheses (Kasi et al., 2025).

Supercritical carbon dioxide ($scCO_2$) is another attractive solvent, offering unique tunable solvency, non-flammability, and ease of removal by simple depressurization. $scCO_2$ has been successfully employed in extraction processes, asymmetric catalysis, and polymerization reactions in pharmaceutical applications, dramatically reducing solvent residues and waste (Green Synthesis and Catalysis, 2025). Its mild critical temperature and pressure make it suitable for thermally sensitive molecules, preserving drug integrity while facilitating greener processing.

Ionic liquids (ILs) and deep eutectic solvents (DESs) have emerged as innovative alternatives that address several limitations of conventional solvents. Ionic liquids are salts that remain liquid at relatively low temperatures and are characterized by negligible vapor pressure, high thermal stability, and excellent solvation abilities. DESs, a subclass of ILs formed by hydrogen bond donors and acceptors, are similarly tunable and biodegradable, often derived from renewable components such as choline chloride and natural acids (Smith et al., 2014). Both ILs and DESs enhance catalyst stability and recyclability, allowing for efficient catalytic cycles and reducing the consumption of hazardous reagents.

Beyond solvent replacement, energy-efficient synthetic methods such as microwave-assisted and ultrasound-assisted synthesis have

revolutionized green chemistry. Microwave irradiation accelerates molecular vibrations, dramatically reducing reaction times from hours to minutes and often enabling solvent-free or aqueous-phase conditions (Green and Sustainable Chemistry, 2024). Ultrasound irradiation enhances mass transfer and reaction rates through acoustic cavitation, further lowering energy demands and improving yields. These technologies also support scaling up by offering precise control over reaction parameters and minimizing side reactions.

Another pivotal green synthesis strategy is mechanochemistry, which involves chemical transformations induced by mechanical force often via ball milling eliminating or drastically reducing the need for solvents altogether. This approach has been successfully applied to the synthesis of active pharmaceutical ingredients (APIs), offering high yields, simplified purification, and reduced waste (Green and Sustainable Chemistry, 2024).

Crucially, biocatalysis integrates enzymatic or whole-cell catalysts into pharmaceutical syntheses, capitalizing on their remarkable selectivity, mild operating conditions, and biodegradability. Enzymatic transformations often proceed under ambient temperature and pressure, reducing the need for hazardous chemicals and energy-intensive steps. This approach is especially beneficial for producing chiral intermediates, a common challenge in drug development (Patel, 2018). Advances in protein engineering and immobilization techniques have expanded enzyme stability and reusability, making biocatalysis a cornerstone of sustainable pharmaceutical manufacturing.

Together, these green synthesis strategies ranging from solvent innovation to cutting-edge energy-efficient and catalytic techniques are transforming pharmaceutical manufacturing. Their adoption supports not only compliance with environmental regulations but also economic advantages through reduced waste treatment costs, improved safety profiles, and enhanced process robustness.

4. BIOCATALYSIS IN GREEN PHARMACEUTICAL SYNTHESIS

Biocatalysis has emerged as one of the most promising and impactful strategies for achieving green and sustainable pharmaceutical synthesis. Utilizing enzymes or whole-cell systems, biocatalysis enables chemical transformations under mild, aqueous conditions, often with exceptional chemo-, regio-, and stereoselectivity. These features not only reduce energy consumption and hazardous waste but also simplify purification and enhance product yields key objectives in green chemistry (Sheldon & Woodley, 2018).

One of the major advantages of biocatalysis is its ability to replace traditional metal-based catalysts, which are often toxic, expensive, and environmentally burdensome. Enzymes such as transaminases, oxidoreductases, hydrolases, and lyases offer a biodegradable, non-toxic alternative capable of catalyzing reactions with minimal by-products and under near-ambient conditions (Bornscheuer et al., 2012). These properties are particularly valuable in the synthesis of chiral drug intermediates, where high enantioselectivity is critical. For example, the enzymatic resolution of racemic alcohols or amines using lipases or ketoreductases has become a standard practice in the synthesis of β-blockers, antidepressants, and statins (Patel, 2011).

Recent innovations in protein engineering and directed evolution have significantly enhanced the stability, activity, and substrate specificity of biocatalysts, allowing them to function in non-natural environments such as organic solvents or high-temperature conditions. This progress has expanded the range of applicable substrates and reactions, bridging the gap between traditional organic synthesis and enzyme-catalyzed transformations (Arnold, 2018). Immobilization technologies have further improved the reusability and operational stability of enzymes, reducing process costs and enabling continuous-flow applications, which are highly desirable for industrial-scale synthesis (Sheldon, 2007).

Several pharmaceutical companies have successfully implemented biocatalysis in commercial drug manufacturing. Notably, Merck's synthesis of sitagliptin, a diabetes drug, was improved by replacing a rhodium-catalyzed asymmetric hydrogenation with a transaminase-catalyzed amination. This change not only eliminated the use of heavy metals but also increased yield and significantly reduced waste generation (Savile et al., 2010). Another example includes the enzymatic preparation of pregabalin intermediates using engineered ω-transaminases, showcasing how tailored biocatalysts can streamline complex synthesis pathways (Truppo, 2017).

The integration of biocatalysis into early drug development and process design is now seen as a strategic imperative. When applied from the outset, enzymes can influence synthetic route selection, reduce the number of steps, and improve overall sustainability. As computational tools and databases for enzyme discovery continue to evolve, the identification of novel biocatalysts for new-to-nature reactions is becoming faster and more efficient, further embedding biocatalysis into modern green chemistry toolkits (Wu et al., 2021).

5. CATALYSIS IN GREEN PHARMACEUTICAL SYNTHESIS

5.1 Overview of Catalysis: Importance in Green Chemistry

Catalysis lies at the heart of green chemistry and plays a crucial role in the sustainable synthesis of pharmaceuticals. By definition, a catalyst is a substance that increases the rate of a chemical reaction without itself being consumed in the process. This ability to accelerate reactions without being used up allows for repeated usage, reducing the need for excess reagents and enabling lower-energy, higher-efficiency processes key principles in green chemistry (Anastas & Warner, 1998).

One of the primary environmental advantages of catalysis is its ability to significantly reduce energy requirements. Catalyzed reactions often proceed under milder temperatures and pressures than their uncatalyzed counterparts. For example, enzymatic or metal-catalyzed reactions can be conducted at room temperature, minimizing the need for energy-intensive heating or cooling, and thereby lowering the carbon footprint of the process (Sheldon, 2012).

In addition to energy efficiency, catalysis improves selectivity, which is especially vital in pharmaceutical synthesis. High chemo-, regio-, and stereoselectivity reduces the formation of unwanted by-products, improving overall yields and decreasing the need for extensive downstream purification. This not only conserves materials and solvents but also diminishes the generation of hazardous waste (Catalysts, 2023). For instance, asymmetric catalysis enables the selective formation of one enantiomer over another crucial in the development of chiral drugs, where biological activity is often enantioselective (Knowles, 2002).

Catalyst recyclability and reusability further enhance the sustainability of catalytic processes. Many homogeneous and heterogeneous catalysts can be recovered and reused multiple times without significant loss in activity, reducing the consumption of valuable metals and raw materials. Immobilized enzymes and supported metal catalysts are increasingly used in industrial processes for this purpose, aligning with the principle of resource efficiency (Ghatge et al., 2025).

From an economic perspective, catalytic processes offer cost savings by decreasing reagent use, reducing waste disposal requirements, and shortening production times. These benefits are particularly relevant in large-scale pharmaceutical production, where raw material costs and environmental compliance are significant concerns (Anastas & Eghbali, 2010).

Moreover, catalysis supports process intensification and miniaturization, enabling reactions to be integrated into continuous-flow systems. These setups improve heat and mass transfer, enhance reaction control, and allow for safer scaling, especially for exothermic or hazardous transformations. Continuous catalysis, particularly using immobilized enzymes or flow-compatible metal catalysts, is now considered a best practice in green manufacturing (Wegner et al., 2012).

5.2 Transition Metal Catalysis in Green Pharmaceutical Synthesis

Transition metal catalysis has long been a pillar of synthetic organic chemistry and plays a central role in the development of many active pharmaceutical ingredients (APIs). Metals such as palladium (Pd), copper (Cu), and ruthenium (Ru) are widely used to catalyze essential bond-forming reactions, including carbon–carbon (C–C) and carbon–nitrogen (C–N) coupling reactions. These transformations are critical for constructing complex drug-like molecules with high selectivity and efficiency (Beller & Bolm, 2004).

One of the most notable contributions is the palladium-catalyzed cross-coupling reactions, including Suzuki–Miyaura, Heck, and Buchwald–Hartwig couplings. These reactions enable the formation of aryl–aryl and aryl–amine linkages under mild conditions with excellent functional group tolerance (Miyaura & Suzuki, 1995).

For example, the Suzuki coupling has been widely adopted in the synthesis of kinase inhibitors, antiviral agents, and other heterocyclic drugs due to its robustness and scalability (Magano & Dunetz, 2011).

Copper catalysis, particularly Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), has become indispensable for synthesizing triazole-containing molecules, many of which exhibit potent bioactivity. This “click” reaction is praised for its modularity, high yields, and biocompatibility, making it ideal for pharmaceutical and medicinal chemistry applications (Hein & Fokin, 2010).

Ruthenium-based catalysts have found applications in olefin metathesis, oxidation, and hydrogenation reactions, offering high efficiency in transforming complex functional groups under mild conditions (Grubbs, 2004). Their tolerance to water and oxygen has made them attractive for large-scale applications, especially in continuous flow or aqueous-phase systems.

However, despite their synthetic utility, transition metal catalysts pose significant environmental and regulatory challenges. Many of these metals are toxic, scarce, and expensive, raising concerns about sustainability and safety, particularly when trace metal residues must be tightly controlled in final pharmaceutical products. Recovery and reuse of metal catalysts, while possible, can be technically complex and not always economically viable (Egorova & Ananikov, 2017).

To address these issues, green chemistry encourages the development of heterogeneous or supported metal catalysts, ligand-free systems, and low-loading catalytic methods that minimize metal leaching and simplify purification. Moreover, integrating these systems into flow reactors allows for better catalyst control, reduced contamination, and improved scalability, thereby making metal catalysis more compatible with green pharmaceutical goals (Porta et al., 2016).

6. ORGANOCATALYSIS: A METAL-FREE ALTERNATIVE

Organocatalysis the use of small organic molecules as catalysts has emerged as a promising alternative to transition metal catalysis in the quest for greener pharmaceutical synthesis. Unlike their metal-based counterparts, organocatalysts are typically non-toxic, biodegradable, and stable under ambient conditions, aligning well with the principles of green chemistry (MacMillan, 2008).

Organocatalysts operate via various mechanisms, including enamine catalysis, iminium catalysis, Brønsted acid/base catalysis, and hydrogen bonding. Commonly used organocatalysts include proline, diarylprolinol silyl ethers, thioureas, and imidazolidinones. These catalysts enable a broad range of reactions such as aldol, Michael, Mannich, and Diels Alder reactions with high enantioselectivity and under mild, aqueous, or solvent-free conditions (Trost, 1991).

One of the major benefits of organocatalysis is the elimination of toxic metal residues, which simplifies downstream purification and reduces environmental risk. This is particularly valuable for drugs intended for parenteral or pediatric use, where trace metal contamination must be avoided. Furthermore, organocatalysts are often air- and moisture-stable, allowing for simpler handling and storage compared to sensitive metal catalysts (Berkessel & Gröger, 2005).

Organocatalysis also supports asymmetric synthesis, making it a key tool in the preparation of chiral intermediates. For example, proline-catalyzed asymmetric aldol reactions have been used to prepare β-hydroxy ketones with high enantioselectivity, while thiourea-based catalysts are employed in nucleophilic additions and cycloadditions to form complex scaffolds (Connon, 2008). These capabilities are vital in drug development, where stereochemistry often dictates biological activity.

Importantly, many organocatalytic reactions are amenable to scale-up and have been successfully implemented in industrial processes. They also integrate well with flow chemistry and multi-component reactions (MCRs), further enhancing their green profile by reducing steps, time, and resource consumption (Sheldon, 2014).

While organocatalysis generally suffers from lower turnover frequencies and higher catalyst loadings compared to metal catalysis, ongoing research in catalyst design, immobilization, and recycling is addressing these limitations. The field continues to evolve rapidly, driven by a growing demand for environmentally benign and economically viable synthetic routes.

Table 2. Comparison of transition metal catalysis vs. organocatalysis in green pharmaceutical synthesis

Parameter	Transition Metal Catalysis	Organocatalysis
Catalysts Used	Pd, Cu, Ru, Ni, Rh, etc.	Small organic molecules (e.g., proline, thioureas, imidazolidinones)
Common Reactions	C–C, C–N, C–O bond formation (e.g., Suzuki, Heck, Buchwald)	Aldol, Michael, Mannich, Diels– Alder, enamine/iminium reactions
Toxicity Concerns	Moderate to high (especially heavy metals like Pd, Rh)	Low toxicity; typically, biodegradable and non-metallic
Residue Control in API	Requires strict purification to meet regulatory limits	Minimal purification required due to low toxicity
Environmental Impact	Depends on metal used and recycling efficiency	Generally, environmentally benign
Reaction Conditions	Often requires inert atmosphere or specific solvents	Mild (ambient temperature, aqueous/solvent-free conditions)
Catalyst Recovery/Reusability	Possible but complex (especially for homogeneous catalysts)	Often challenging but improving with immobilized systems
Metal-Free Process	No	Yes
Enantioselectivity	Achievable with chiral ligands	High with chiral organocatalysts
Cost of Catalyst	Often expensive (especially noble metals)	Generally lower cost
Industrial Applications	Widely used; scalable with proper controls	Increasingly adopted; suitable for flow and green processes
Green Chemistry Score	Moderate (depends on metal, ligands, and process design)	High (due to metal-free, low-toxicity profile)

7. CASE STUDIES IN INDUSTRIAL GREEN SYNTHESIS

Industrial implementation of green chemistry principles has shifted from conceptual advocacy to practical necessity in pharmaceutical manufacturing. Regulatory pressures, environmental sustainability goals, and cost efficiency have driven leading pharmaceutical companies to adopt greener synthetic strategies. This section presents selected real-world case studies that highlight the integration of green synthesis, particularly emphasizing improvements in atom economy, solvent use, energy reduction, and environmental impact minimization.

7.1 Sitagliptin – Enzymatic Amination Replacing Metal Catalysis

Merck's synthesis of sitagliptin, a DPP-4 inhibitor for type 2 diabetes, is a landmark example of green biocatalysis in industry. Originally, the synthesis involved a rhodium-catalyzed asymmetric hydrogenation, which posed toxicity concerns and required high pressure and costly ligands. In 2010, Merck replaced this step with an engineered transaminase enzyme, enabling enantioselective amination under mild, aqueous conditions (Savile et al., 2010).

This biocatalytic approach:

- Improved yield from 66% to 83%
- Eliminated the use of heavy metals
- Reduced waste by over 19%
- Enabled water as a benign solvent

The process won the EPA Presidential Green Chemistry Challenge Award, underscoring the industrial and environmental impact of enzyme-driven synthesis (EPA, 2010).

7.2 Atorvastatin – Asymmetric Hydrogenation and Flow Synthesis

Pfizer's blockbuster drug atorvastatin (Lipitor) relies heavily on asymmetric hydrogenation for the synthesis of its chiral intermediates. Early processes required high catalyst loadings and generated metal waste. Subsequent development introduced ruthenium and rhodium-catalyzed hydrogenations with enhanced turnover numbers (TONs) and ligand recycling, reducing both metal consumption and purification costs (Magano & Dunetz, 2011).

Furthermore, process intensification was achieved through flow chemistry, improving heat transfer and enabling safer scale-up. This

combination reduced waste, improved throughput, and enhanced safety.

7.3 Artemisinin Semi-Synthetic Bio-synthesis Using Fermentation

Artemisinin, a key antimalarial compound, was historically extracted from the plant *Artemisia annua*, which suffered from seasonal variability and high cost. A collaborative effort led by Amyris and Sanofi resulted in the semi-synthetic production of artemisinin using engineered *Saccharomyces cerevisiae* yeast strains to biosynthesize artemisinic acid, which is chemically converted to artemisinin (Ro et al., 2006).

This innovation:

- Enabled year-round, scalable production
- Reduced dependency on agricultural land
- Lowered production costs and stabilized global supply
- Was supported by the Bill & Melinda Gates Foundation for global health access

This case exemplifies how synthetic biology, integrated with green chemistry, can solve complex pharmaceutical supply challenges.

7.4 Ibuprofen – The BHC Green Route

The traditional synthesis of ibuprofen involved a six-step process with poor atom economy and large amounts of waste. The Boots–Hoechst–Celanese (BHC) process, developed in the 1990s, reduced the synthesis to three steps with >99% atom economy using catalytic hydrogenation and acylation (Brown & Boström, 2016).

Key improvements include:

- Use of heterogeneous catalysts (e.g., Pd/C)
- Elimination of stoichiometric oxidants
- Minimized solvent use
- Significant reduction in by-product formation

This became one of the earliest and most celebrated examples of industrial green synthesis.

7.5 Brivaracetam – Continuous Flow and Catalysis Integration

UCB Pharma's development of brivaracetam, an antiepileptic drug, incorporated flow synthesis, catalysis, and solvent recycling to reduce environmental impact. The synthesis employed Buchwald–Hartwig cross-coupling, optimized under continuous flow conditions, significantly reducing solvent volume and improving product purity (Plutschack et al., 2017).

The green features included:

- Use of low catalyst loadings
- Solvent recovery exceeding 80%
- Elimination of hazardous reagents
- Streamlined downstream processing

8. SUSTAINABILITY METRICS AND LIFE CYCLE ASSESSMENT IN GREEN CHEMISTRY

Quantifying the environmental impact of chemical processes is essential to ensure that "green" innovations deliver measurable improvements. In pharmaceutical synthesis, sustainability metrics and Life Cycle Assessment (LCA) are powerful tools for evaluating the environmental, economic, and social performance of synthetic routes. These approaches support decision-making in research, development, and manufacturing by identifying opportunities to reduce waste, energy consumption, and emissions.

8.1 Green Chemistry Metrics

Several quantitative metrics have been developed to assess the greenness of chemical reactions and processes. Key among them are in List 1.

These metrics are most informative when used in combination, as a single number rarely captures the full sustainability profile of a process.

8.2 Process Mass Intensity (PMI): A Preferred Industry Metric

PMI is one of the most widely adopted metrics in the pharmaceutical industry due to its simplicity and broad applicability. Unlike the E-factor, PMI accounts for all materials used in the process, including solvents and auxiliary agents, offering a more holistic view of material efficiency. Companies such as Pfizer, GlaxoSmithKline, and AstraZeneca now use PMI dashboards in early-stage development to guide greener route selection (Roschangar et al., 2017).

A PMI value below 50 is considered good for active pharmaceutical ingredient (API)

manufacturing, while <10 is targeted in highly optimized processes. Strategies to reduce PMI include:

- Switching to solvent-free or aqueous systems
- Minimizing work-up steps
- Integrating flow chemistry and telescoped reactions
- Reducing purification stages

8.3 Life Cycle Assessment (LCA)

While green chemistry metrics focus on the process itself, Life Cycle Assessment (LCA) evaluates the environmental footprint across the entire life cycle from raw material extraction to manufacturing, distribution, use, and disposal. This systems-level approach is crucial for identifying hidden environmental costs or trade-offs that process metrics may overlook (Jiménez-González et al., 2011).

Key LCA Stages in Pharma:

1. Raw Material Sourcing – impact of mining, agriculture, or fermentation
2. Process Manufacturing – energy, solvents, emissions, waste
3. Formulation and Packaging – water use, plastics, recyclability
4. Distribution and Use – transport emissions, shelf life
5. End-of-Life – degradation, toxicity of waste or by-products

LCA tools such as GaBi, SimaPro, and Open LCA are used to model these stages based on inventory databases (e.g., Ecoinvent). LCA can reveal scenarios where a "green" reagent may have a high environmental cost due to non-renewable sourcing or toxic degradation products (Wernet et al., 2016).

8.4 Integration into Decision-Making

For maximum impact, sustainability metrics and LCA must be integrated early in the development pipeline not just at scale-up. Several pharmaceutical companies now employ Green Chemistry Performance Indicators (GCPIs) and toolkits to guide synthetic planning, optimize supply chains, and meet ESG goals.

The ACS Green Chemistry Institute Pharmaceutical Roundtable provides free calculators, solvent selection guides, and LCA resources to support greener synthesis planning and metric benchmarking (ACS Green Chemistry Institute, n.d.).

9. CHALLENGES AND FUTURE OUTLOOK IN GREEN PHARMACEUTICAL SYNTHESIS

Despite the considerable progress in developing and adopting green chemistry strategies within the pharmaceutical industry, several practical, technical, economic, and regulatory challenges still hinder the full realization of sustainable drug development. This section discusses these barriers and provides insights into emerging trends and future directions to overcome them.

9.1 Current Challenges

1. Technical Limitations of Green Reagents and Catalysts

While enzymatic, organocatalytic, and heterogeneous systems offer green advantages, they often suffer from limited substrate scopes, lower turnover numbers, and stability issues. For example, many biocatalysts cannot withstand harsh industrial conditions such as high temperatures, organic solvents, or extremes of pH. Similarly, organocatalysts often require higher loadings and longer reaction times compared to traditional metal-based systems (Bornscheuer et al., 2012).

2. Scalability and Process Integration

Processes that work well on a laboratory scale may encounter scaling issues in production. Flow chemistry, biocatalysis, and telescoped reactions often require reengineering of equipment, specialized training, and process control systems that may not be readily available or economically feasible for all companies (Hartman et al., 2011).

3. Regulatory and Quality Concerns

Incorporating new green methodologies must comply with strict Good Manufacturing Practice (GMP) and regulatory guidelines. Metal contamination, enzyme residues, or novel reaction by-products may require additional validation or purification, increasing complexity and cost (ICH, 2022). Additionally, change management for approved drug processes is slow and tightly regulated, limiting green upgrades for existing drugs.

Table 3. Case studies in industrial green pharmaceutical synthesis

Drug	Company	Green Strategy Applied	Key Improvements	Reference
Sitagliptin	Merck	Enzymatic transaminase replacing Rh- catalysis	↑ Yield (66% → 83%), no heavy metals, aqueous medium, ↓ waste by 19%	(Savile et al., 2010, EPA, 2010)
Atorvastatin	Pfizer	Asymmetric hydrogenation, flow chemistry	High enantioselectivity, catalyst recycling, safer scale-up, ↓ cost	(Magano & Dunetz, 2011)
Artemisinin	Amyris / Sanofi	Biosynthesis via engineered yeast + chemical conversion	Stable year-round supply, renewable feedstocks, ↓ agricultural dependency	(Ro et al., 2006)
Ibuprofen	Boots– Hoechst–Celanese (BHC)	Shortened synthesis using catalytic steps	Atom economy >99%, fewer steps, heterogeneous catalysis, ↓ by-products	(Brown & Boström, 2016)
Brivaracetam	UCB Pharma	Flow chemistry, Buchwald–Hartwig cross-coupling	Low catalyst loading, solvent recycling (>80%), safer and greener workup	(Plutschack et al., 2017)

List 1. Several quantitative metrics with their definition and purpose

Metric	Definition / Purpose
Atom Economy (AE)	Measures the proportion of reactant atoms incorporated into the final product (Trost, 1995).
E-factor	Calculates the mass of waste per mass of product. Lower values indicate cleaner processes (Sheldon, 2007).
Process Mass Intensity (PMI)	Total mass of all materials used (solvents, reagents, catalysts) per kg of product (Constable et al., 2002).
Carbon Efficiency	Ratio of carbon in the final product to carbon in all reactants (Kerton & Marriott, 2013).
EcoScale	Scores reactions based on yield, safety, cost, and environmental impact (Van Aken et al., 2006).

Table 4. Summary of sustainability metrics and life cycle assessment tools in green chemistry

Metric / Tool	Purpose	Key Features / Benefits
Atom Economy (AE)	Evaluates how efficiently atoms of reactants are incorporated into products	Encourages fewer by-products; ideal is 100% (Trost, 1995)
E-factor	Measures waste generated per unit of product	Lower E-factor indicates a cleaner process (Sheldon, 2007)
Process Mass Intensity (PMI)	Total mass of all materials (reagents, solvents, etc.) per kg of product	Holistic, widely used in pharma industry (Constable et al., 2002)
Carbon Efficiency	Measures how much carbon from reactants is retained in the product	Focuses on minimizing carbon waste (Kerton & Marriott, 2013)
EcoScale	Semi-quantitative score based on yield, cost, safety, and environmental impact	Useful in comparing alternative routes (Van Aken et al., 2006)
Life Cycle Assessment (LCA)	Evaluates total environmental impact from raw material to disposal	System-level analysis; identifies upstream and downstream impacts (Jiménez-González et al., 2011, Wernet et al., 2016)
Green Chemistry Performance Indicators (GCPIs)	Internal benchmarks for sustainability across projects	Used by pharma companies for early- stage decision-making (Roschangar et al., 2017, ACS Green Chemistry Institute, n.d.)
ACS GCI PR Toolkit	Tools and calculators for evaluating and improving green processes	Industry-standard resources for synthesis planning (ACS Green Chemistry Institute, n.d.)

4. Economic and Market Constraints

While green chemistry is cost-effective long-term, the upfront investment in R&D, training, and infrastructure can be significant. Small and medium-sized enterprises (SMEs) may struggle with resource limitations. Furthermore, market-driven priorities, such as speed to market or IP protection, often override sustainability considerations during early development (Sheldon, 2008).

10. LIMITED AWARENESS AND CULTURAL RESISTANCE

Many chemists still lack sufficient training in green chemistry metrics, tools, and thinking. In some environments, organizational inertia or risk aversion can hinder the adoption of unfamiliar green strategies, even when benefits are clear (Curzons et al., 2001).

10.1 Future Outlook

Despite these challenges, several positive trends indicate a promising future for green pharmaceutical synthesis:

1. Artificial Intelligence and Digital Tools

The integration of AI, machine learning (ML), and cheminformatics is accelerating green chemistry innovation. These technologies are increasingly used to predict reaction outcomes, optimize catalyst selection, and design greener routes with improved efficiency and lower environmental impact (Segler et al., 2018).

2. Advancements in Biocatalysis and Enzyme Engineering

Recent breakthroughs in directed evolution and enzyme immobilization have significantly expanded the applicability of biocatalysts. Enzymes are now being engineered for robustness, substrate tolerance, and solvent compatibility, making them more viable for industrial-scale synthesis (Arnold, 2019).

3. Circular Chemistry and Renewable Feedstocks

There is a growing push toward circular chemistry, where waste is reused, and bio-based or recycled feedstocks replace petrochemical derivatives. Advances in biomass valorization and CO_2 utilization offer new opportunities for greener, more sustainable starting materials (Clark et al., 2012).

4. Policy and Corporate Commitments

Stricter environmental regulations and ESG (Environmental, Social, Governance) reporting standards are compelling pharmaceutical companies to adopt green processes. Several large firms now publish sustainability reports and adhere to carbon-neutral or zero-waste goals, accelerating the institutional adoption of green chemistry (GSK, 2024).

5. Education and Workforce Development

Green chemistry is becoming a core topic in academic and industrial training programs. Integration into curricula, workshops, and industry consortiums (e.g., the ACS Green Chemistry Institute Pharmaceutical Roundtable) is building a new generation of chemists equipped to design and implement sustainable processes (Anastas & Warner, 1998).

11. CONCLUSION

Green chemistry has evolved from a theoretical concept into a vital framework that is actively transforming pharmaceutical synthesis. The application of green principles ranging from atom economy and solvent selection to biocatalysis and continuous flow processes has demonstrated significant potential to enhance efficiency, reduce environmental impact, and improve the safety and sustainability of drug manufacturing.

This review has highlighted the integration of green metrics, the use of renewable feedstocks, solvent-free systems, biocatalysis, organocatalysis, and sustainable catalysis as core elements shaping modern pharmaceutical processes. The inclusion of case studies such as sitagliptin, ibuprofen, and artemisinin demonstrates that green chemistry is not only scientifically viable but also economically beneficial and scalable.

However, substantial challenges remain, including technical barriers, regulatory hurdles, and economic constraints. Overcoming these will require continued innovation in catalyst design, broader adoption of AI-driven route planning, and institutional support for greener infrastructure and education. Furthermore, the implementation of Life Cycle Assessment (LCA) and sustainability

metrics will remain crucial for evaluating the long-term environmental impact of pharmaceutical synthesis.

Looking forward, the pharmaceutical industry is increasingly aligning with sustainability goals, supported by stricter environmental regulations and growing societal demand for eco-conscious practices. As technology advances and cross-disciplinary collaborations expand, green chemistry is set to become the default standard for pharmaceutical innovation, not just an alternative pathway.

By embedding green principles into the core of drug development, the pharmaceutical industry can simultaneously drive scientific excellence and environmental stewardship paving the way for a more sustainable, responsible future in global healthcare.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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