RESEARCH PAPER

Green Chemistry Approaches in API Synthesis: Methods and Industrial Impact.

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ABSTRACT
Active Pharmaceutical Ingredients (API) production is a resource-intensive process, which is traditionally founded on the utilisation of toxic reagents, large volumes of solvents, and multistep reaction pathways, which represent severe environmental and economic issues. The increasing regulatory pressure and the global sustainability goals have made green chemistry a powerful paradigm of transforming the pharmaceutical manufacturing process into a more responsible one. The review addresses the current trends in green chemistry approaches applied in the production of API, particularly their approaches and their impact on the industry. The selection of green solvents and solvent minimization, catalytic and biocatalytic transformations, renewable feedstocks and safer reagents, process intensification and continuous manufacturing technologies are some of the important strategies discussed. The importance of quantitative measures of sustainability, e.g. E-factor and Process Mass Intensity, and the incorporation of life cycle assessment tools are identified as critical in assessing and informing sustainable process design. Industrial views are highlighted, showing how the implementation of green chemistry leads to waste reduction, better process efficiency, cost-saving, and resilience of supply-chain. The issues of scalability, economic investment, and regulatory compliance are also covered, as well as the emerging trends, including digital green-by-design tools and integrated manufacturing platforms. This literature review explains the importance of green chemistry in facilitating sustainable, efficient, and sustainable API production and offers an indication to researchers, process chemists, and industry stakeholders interested in developing more environmentally responsible methods of producing pharmaceuticals.
Keywords: Green chemistry; Active pharmaceutical ingredients; Sustainable API synthesis; Process intensification; Continuous manufacturing; Industrial sustainability.
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INTRODUCTION

Pharmaceutical formulations are founded on Active Pharmaceutical Ingredients (APIs) that is the inseparable component of the contemporary health care systems in the globe. They participate in the curative action of drugs and are highly useful in prevention, diagnosis and treatment of an enormous number of diseases. With the pharmaceutical market in the world steadily increasing, the demand of APIs has also increased tremendously and this has witnessed an increase in the manufacturing processes in both the developed and emerging economies. Pharmaceuticals, particularly API, is a complex multi-phase process, which may be described by complex chemical reactions, high purity, and strict regulatory measures. As a result, the pharmaceutical industry has turned the efficiency, safety, and sustainability of API production into a fundamental concern (Kar et al., 2021; Ahsan et al., 2020). Besides their clinical value, APIs represent a significant economic segment of pharmaceutical value chain and, therefore, the improvement of their manufacturing processes is critical to the health of the population and the competitiveness of the industrial sector (Valavanidis and Vlachogianni, 2012).Traditional API synthesis pathways are often believed to be linked with significant issues in terms of environmental impact and operation. The conventional pharmaceutical production process is based on the use of stoichiometric reagents, dangerous chemicals, and a lot of organic solvents, which results in the excessive generation of waste and uses a lot of energy. Statistical measures like the E- factor and Process Mass Intensity (PMI) indicate that pharmaceutical processes particularly API production produce a lot more waste per kilogram of product compared to the majority of other chemical industries. This waste burden does not only raise the cost of production but also causes environmental pollution and depletion of the resources (Sheldon, 2007). Further, most of the classical synthetic processes require numerous protection-deprotection cycles, low atom economy, and inefficient reaction pathways, which further increases their impact on the environment (Jiménez-González et al., 2011). The release of solvent waste and by-products, and emissions of energy-intensive processes, has increased a growing concern of the sustainability of conventional API production in the long term (Fortunak, 2009).These issues have increased the necessity to change the paradigm to a more sustainable and environmentally friendly system of pharmaceutical production. Sustainable pharmaceutical manufacturing is meant to strike a balance

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between economic viability and environmental protection as well as social responsibility. Green chemistry has in this regard become a revolutionary concept that can be used to re-model chemical processes in order to reduce the amount of waste, toxicity, and resource efficiency. Green chemistry has the guiding principles of prevention rather than remediation, safer solvents and reagents, energy conservation and the development of naturally benign chemical reactions (Anastas and Warner, 2000). These principles will give the opportunity to reduce the cost of production in the case of the pharmaceutical industry, strengthen the process and improve regulatory compliance and meet the rising environmental and societal demands (Dunn et al., 2010). Sustainability is a relatively new strategic concern of pharmaceutical firms, both due to regulatory pressure and corporate responsibility goals and an emerging emphasis on the significance of environmentally friendly supply chains (Konwarh, 2025).

The application of the green chemistry concept in the production of the API has become very popular over the past 2 decades. It has been demonstrated by the invention of catalysis, solvent selection, biocatalysis, continuous processing and other reaction technologies that more sustainable processes can, in most cases, be more selective, higher yielding and less wasteful than conventional processes. Green chemistry is not viewed as an environmental initiative anymore but a powerful driver of innovation that can enhance the efficiency of the process and product quality. A number of publications have highlighted the possibility to integrate green synthetic methods into the production of APIs without compromising regulatory and economic sustainability (Kar et al., 2021). The implementation of green chemistry principles is consistent with the transformation of the pharmaceutical industry to quality-by-design and green-by-design paradigms, in which sustainability is considered at the initial stage of the development of the process (Stefanache et al., 2025). Notably, industrial applications have helped the development of green chemistry in the pharmaceutical industry that has proven to be practically relevant and valuable in the long term (Fortunak, 2009).

Due to the active development of sustainable technologies and the growing interest in the environmentally responsible production, there is a strong necessity of thorough studies which would summarize the recent advances in the field of green API synthesis. This review will critically analyze the strategies of green chemistry used in the synthesis of APIs with special reference to the major strategies as solvent optimization, catalysis, biocatalysis, process intensification, and continuous manufacturing. Besides that, the review examines the industrial effect of the approaches, which include the fact that they have helped to decrease the burden on the environment and increase the efficiency of the processes, as well as ensure compliance with the regulatory aspects. Through the integration of the current events and industrial thinking, this article aims to give researchers, process chemists and industry stakeholders a consistent view of current trends and future perspectives in sustainable API manufacturing.

2. Principles of Green Chemistry in Pharmaceutical Synthesis

Green chemistry can be applied to pharmaceutical synthesis to offer a logical approach towards reducing the environmental and societal effects of Active Pharmaceutical Ingredient (API) production. Green chemistry, which is officially defined by twelve principles, focuses on designing chemical processes that minimize or avoid the use and production of hazardous substances during the product life cycle (Anastas and Warner, 2000). Such principles cover the most important issues of chemical synthesis, such as the prevention of waste, atom economy, safer solvents, energy efficiency, and inherently benign reaction conditions. The implementation of these principles has now been considered critical in the production of sustainable and economically viable API, especially in the pharmaceutical manufacturing industry where complex multistep syntheses are prevalent.

Atom economy is one of the twelve principles, which is especially important to enhance the inherent efficiency of synthetic pathways. Atom economy was introduced as a quantitative tool of the degree to which reactants are converted into the final product and therefore, the atom economy is an encouragement to select reactions that make the most out of the material and the least out of the by-products (Trost, 1991). High atom economy is particularly applicable to the synthesis of APIs, where low-yielding steps and overprotective-group methods can cause the generation of a large amount of waste. Pharmaceutical chemists can thus save a lot of resources by focusing on reactions like catalytic reactions, rearrangements, and addition reactions without compromising the quality of the product or regulatory standards.

Reduction of waste is another principle of green chemistry in pharmaceutical production. The pharmaceutical industry is also reported to produce a disproportionately large amount of waste compared to the production of the products, especially API production. The E-factor which is the ratio of waste to product produced has been widely used as a measure of environmental performance in chemical processes. It has been demonstrated that in many cases the traditional API syntheses have orders of magnitude higher E-factors than bulk chemical industries (Sheldon, 2007). The minimization of the E-factor by optimizing the processes, recycling of solvents and catalytic transformations has thus become a major goal in the development of green pharmaceuticals.

Although measures like atom economy and E-factor are useful, they do not give good insights when applied alone. In order to overcome this drawback, more detailed mass-based measures have been created, the most famous of which is Process Mass Intensity (PMI). PMI is the ratio of the total mass of all materials consumed in a process to the mass of the end product and is especially appropriate in the multistep API syntheses which are complex. The prevalence of the PMI use in the pharmaceutical industry has facilitated more open benchmarking of the process sustainability at different development stages and manufacturing levels (Benison and Payne, 2022). Moreover, PMI is not only limited to reaction steps but also has auxiliary operations like equipment cleaning, which confirms its applicability to full-scale industrial evaluation (Rose et al., 2022).

Recent developments in predictive and design-based green metrics have enhanced the concept of sustainability in the early process development even more. Computerized tools like the PMI Predictor help chemists to approximate what the environmental footprint of a proposed synthetic route might be, prior to laboratory/pilot-scale execution. These tools can be used to make informed decisions by enabling comparative analysis of alternative pathways and foster green-by-design approaches to API synthesis (Borovika et al., 2019). This is because the predictive metrics that are considered during the initial stages of route selection minimize the chances of

expensive redesign in the later phases and makes the sustainability objectives consistent with time and cost limitations.

Industrially and regulation wise, green metrics have become more and more important, as pharmaceutical companies strive to show environmental responsibility and at the same time have strong supply chains. The green metrics standardization and harmonization have been highlighted as industry-led initiatives, especially those organized on the basis of collaborative platforms, to promote cross-company comparisons and best-practice exchange. Industrial stakeholders suggest that not only are PMI and E-factor the means of environmental evaluation, but they also lead to the emergence of innovations, cost minimization, and the avoidance of risks (Koenig et al., 2019). In more recent times, sustainability policies formulated by industry consortia have highlighted the importance of green metrics in the determination of long-term API manufacturing policies and regulatory participation (Colberg et al., 2025).

The principles of green chemistry with the support of quantitative measures and predictive instruments provide a good foundation on the basis of which the API synthesis process can be made more sustainable. Their successful implementation is a comprehensive solution that includes of molecular design, process optimization and industrial alliance. With the constant changing regulatory requirements and social pressures towards sustainability, the principles and metrics of green chemistry will still take center stage in the future of pharmaceutical manufacturing. Table 1 provides a summary of the concepts of green chemistry and quantitative measures applicable in sustainable production of active pharmaceutical ingredients (API).

Table 1. Key Green Chemistry Principles and Metrics Relevant to API Synthesis

Green Chemistry Principle / Metric	Description	Relevance to API Synthesis	Key References
Twelve Principles of Green Chemistry	Framework for designing safer and more sustainable chemical processes	Guides holistic improvement of API synthesis routes	Anastas & Warner (2000)
Atom Economy	Measures incorporation of reactants into final product	Encourages efficient, low-waste synthetic reactions	Trost (1991)
E-factor	Ratio of waste generated to product formed	Highlights excessive waste in pharmaceutical processes	Sheldon (2007)
Process Mass Intensity (PMI)	Total mass of materials used per mass of API produced	Enables benchmarking of multistep API processes	Benison & Payne (2022); Rose et al. (2022)
Predictive Green Metrics	Early-stage estimation of environmental impact	Supports green-by-design route selection	Borovika et al. (2019)
Industrial Sustainability Metrics	Standardized metrics for industrial decision-making	Aligns sustainability with supply-chain robustness	Koenig et al. (2019); Colberg et al. (2025)

Figure 1 shows schematic illustration of green chemistry principles and associated sustainability metrics guiding environmentally responsible active pharmaceutical ingredient (API) synthesis.

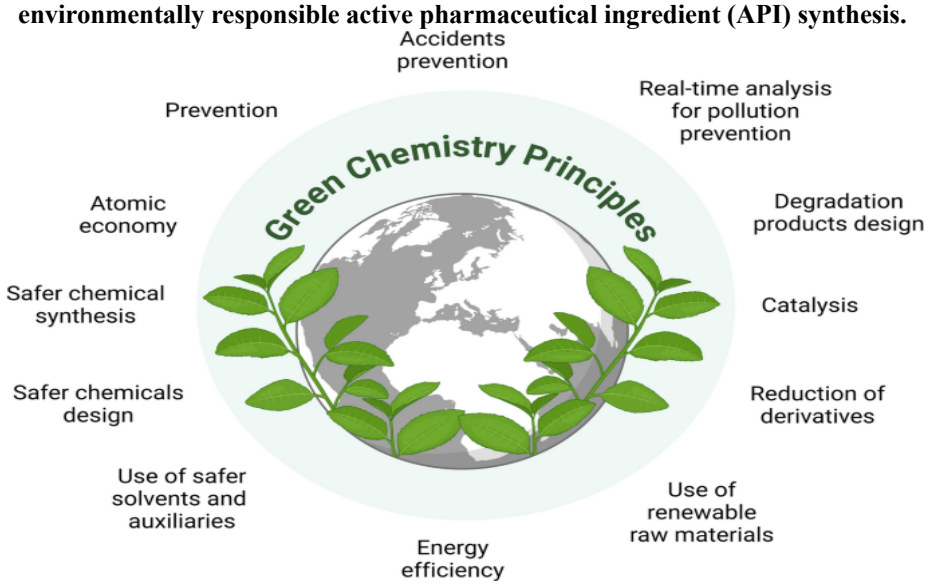

Figure 1. Principles and sustainability metrics of green chemistry applied to API synthesis (Kurul et al., 2025)

3. Green Synthetic Strategies for API Production

The effective use of green chemistry in the synthesis of Active Pharmaceutical Ingredient (API) depends on the introduction of new synthetic approaches that do not harm the environment and still achieve efficiency, safety, and regulatory compliance. Of these methods, solvent

optimization, catalysis, biocatalysis, and other enabling technologies have become important contributors to sustainable manufacturing of pharmaceuticals. All these methods help to deal with significant waste, toxicity, and energy usage in traditional API manufacturing and is a step in the direction of more environmentally friendly and resource-efficient chemical reactions. Figure 2 combined the illustration of green synthetic strategies used at each stage of the API production lifecycle, including solvent optimization, catalysis and biocatalysis, alternative enabling technologies and sustainable scale-up.

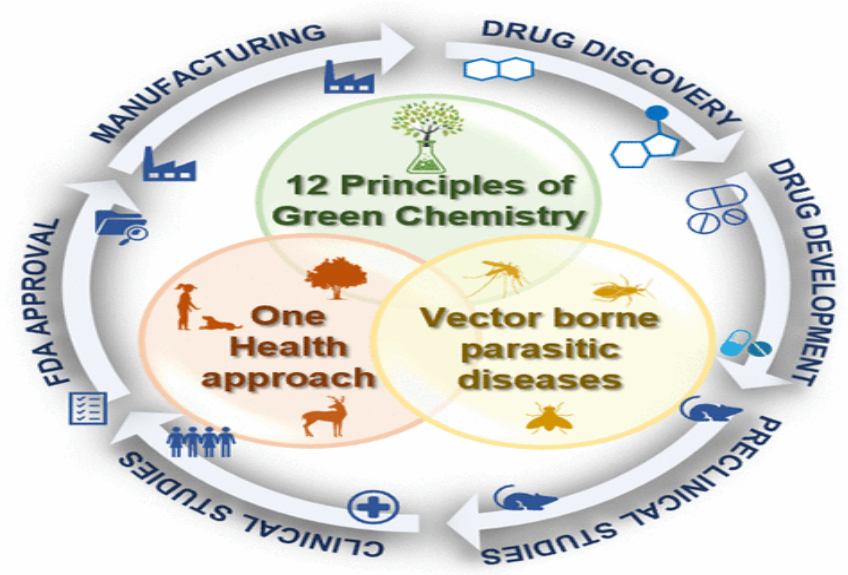

Figure 2. Integrated green synthetic strategies across the API production lifecycle (Martinengo et al., 2024)

3.1 Solvent Selection and Solvent Reduction

The percentage of material input and waste produced during pharmaceutical production, especially in API production, is a significant percentage of solvents. The traditional organic solvents like chlorinated hydrocarbons, aromatic solvents, and polar aprotic solvents are very toxic, volatile and have long-term effects on the environment and are therefore dangerous to the environment and health (Valavanidis and Vlachogianni, 2012). In addition, solvent-intensive manufacturing processes also play a significant role in the total environmental impact of pharmaceutical manufacturing, as evidenced by life cycle assessment of API production (Kar et al., 2021). As a result, the solvent choice and minimization have become the main areas of green process optimization.

In order to overcome these issues, systematic green solvent selection models have been created to direct chemists to the use of safer and more sustainable solvents. The solvent selection guides are based on environmental, health, and safety (EHS) criteria that allow systematic analysis of solvents and encourage the replacement of hazardous solvents with greener alternatives, including water, ethanol, bio-based solvents, and supercritical fluids (Byrne et al., 2016; Prat et al., 2016). The quantitative solvent assessment tools have facilitated the making of informed decisions during the process of route design and process development (Piccione et al., 2019). Besides the replacement of solvents, there are methods aimed at minimising solvent usage such as solvent recycling, telescoped reactions, and solvent-free reactions that have demonstrated significant amounts of waste generation and cost of operation (Dunn et al., 2010). The broader sustainability initiative of supply chain resilience and environmental stewardship is also associated with solvents minimization (Koenig et al., 2019). The summary of the green solvent selection and solvent reduction methods applied in the sustainable API synthesis is presented in Table 2.

Table 2. Green solvent strategies and their relevance to sustainable API synthesis

Strategy	Description	Sustainability Benefit	Key References
Green solvent selection	Use of low-toxicity and renewable solvents	Reduced environmental and health risks	Byrne et al. (2016); Prat et al. (2016)
Solvent assessment tools	Quantitative EHS-based solvent ranking	Informed process design	Piccione et al. (2019)
Solvent minimization	Reduction or elimination of solvent use	Lower waste and PMI	Dunn et al. (2010); Koenig et al. (2019)

3.2 Catalysis in Green API Synthesis

Catalysis is significant in the sustainability of API synthesis to enhance the efficiency, selectivity, and atom economy of the reaction. Catalytic reactions are also used to reduce the utilisation of stoichiometric reagents and minimise the generation of by-products, thereby lowering the quantity of

waste and energy expenditure (Kar et al., 2021). The use of homogeneous and heterogeneous catalysts in green pharmaceutical synthesis has been widely adopted though there has been an increased interest in catalysts recyclability and reduction of toxicity.

The recent advances on oxidative and transition-metal-catalyzed reactions have enabled the synthesis of APIs and their intermediates in a more environmentally friendly manner. These catalytic systems can be performed under less demanding conditions and use environmentally friendly oxidants, which is a major advantage over the conventional ones (García-Fernández et al., 2023). Simultaneously, electrochemical catalysis has been considered an alternative to reagents that are hazardous, and instead of using reagents, electrons as clean redox agents are used. Electrochemical reactions have shown efficiency and selectivity in API production and minimal chemical wastes and enhanced safety of the process (Cantillo, 2022; Ghosh et al., 2024). Table 3 overview of catalytic methods to improve efficiency and sustainability in the production of green API.

Table 3. Catalytic approaches contributing to green API synthesis

Catalytic Approach	Key Features	Green Advantage	Key References
Transition-metal catalysis	High selectivity and efficiency	Improved atom economy	Kar et al. (2021); García-Fernández et al. (2023)
Oxidative catalysis	Mild oxidants and conditions	Reduced hazardous waste	García-Fernández et al. (2023)
Electrochemical catalysis	Electron-driven transformations	Minimal reagent waste	Cantillo (2022); Ghosh et al. (2024)

3.3 Biocatalysis and Enzymatic Transformations

Biocatalysis has proven to be a potent green technology in the production of API that has remarkable chemo-, regio-, and enantioselectivity under mild reaction conditions. Transformations catalyzed by enzymes are especially useful in the production of chiral APIs, in which a traditional chemical procedure can take several steps and produce a lot of waste (Zhang et al., 2024). Enzyme reactions can be conducted at ambient temperature and pressure, which saves a lot of energy (Kar et al., 2021).

The intersection of the principles of biocatalysis and green chemistry has been growing at a pace, which has been facilitated by the progress in the field of enzyme engineering and process optimization. The photo-biocatalytic cascades and multi-enzymatic systems have extended the field of sustainable pharmaceutical production further (Özgen et al., 2021). These advancements prove that enzymatic transformations may be easily integrated with green manufacturing approaches, which can serve as the means to achieve environmental and economic goals (Stefanache et al., 2025). Table 4 shows the key functions and benefits of biocatalysis in the manufacture of APIs that are environmentally friendly.

Table 4. Role of biocatalysis in sustainable API synthesis

Biocatalytic Feature	Benefit	Application in APIs	Key References
High enantioselectivity	Reduced purification steps	Chiral API synthesis	Zhang et al. (2024)
Mild reaction conditions	Energy efficiency	Sensitive intermediates	Kar et al. (2021)
Integrated biocatalytic systems	Enhanced sustainability	Green process design	Özgen et al. (2021); Stefanache et al. (2025)

3.4 Alternative and Enabling Technologies

Other reaction technologies have greatly increased the green API synthesis toolbox. Solvents Solvents Solvent-free or solvent-minimized reactions (due to the input of mechanical energy) have shown significant solvent consumption and waste reduction (Fantozzi et al., 2023). Recent developments in the design of mechanochemical reactors and the control of reactions have expanded its range of use in pharmaceutical manufacturing (Kubota, 2023).

Mechanochemistry has been shown to be industrially relevant, as comparative studies have shown that it can be more efficient and less harmful to the environment than conventional solution-based approaches in the preparation of various APIs (Leitão, 2024; Pattanayak et al., 2025). To choose enabling technologies, it is necessary to have systematic evaluation frameworks that take into account technical feasibility, sustainability gains, and economic feasibility, so that they will be adopted at the industrial level (Georgiadis et al., 2013). Table 5 provides other and enabling technologies that are in favor of green and solvent-minimized API synthesis.

Table 5. Alternative and enabling technologies for green API synthesis

Technology	Principle	Industrial Relevance	Key References
Mechanochemistry	Solvent-free synthesis via mechanical energy	Reduced waste and solvent use	Fantozzi et al. (2023); Kubota (2023)

Mechanochemical API production	Scalable solid-state reactions	Industrial validation	Leitão (2024); Pattanayak et al. (2025)
Technology selection frameworks	Multi-criteria decision tools	Informed process adoption	Georgiadis et al. (2013)

4. Renewable Feedstocks and Green Reagents

Switching to renewable feedstocks and green reagents is a key aspect of sustainable Active Pharmaceutical Ingredient (API) synthesis. Traditional pharmaceutical production is largely based on fossil-based raw materials and toxic reagents, which are factors in resource depletion, environmental pollution and the issue of long-term sustainability. Green chemistry encourages the substitution of such substances with renewable, safer, and more efficient ones that do not harm the environment, preserve the quality of the product, and do not violate the regulations. The inclusion of renewable feedstocks and green reagents in the API synthesis process is also beneficial to environmental targets, as well as supply-chain resilience and economic sustainability (Kar et al., 2021).

Renewable and bio-based reagents have received growing interest as plausible alternatives to petrochemicals-based starting materials in the synthesis of pharmaceuticals. Biomass-derived platform chemicals, carbohydrates, organic acids, alcohols, and other renewable feedstocks have a great advantage, which is a smaller carbon footprint and a higher life-cycle sustainability. Formic acid has been one of these and has become a useful renewable reagent because it is low in toxicity, biodegradable and also has a dual characteristic of being a source of hydrogen and a reducing agent. Its use in catalytic hydrogenation, transfer hydrogenation, and C-C bond-forming reactions shows that it can be used to substitute more dangerous reagents that have been used traditionally to prepare APIs (Liu et al., 2015). Industrially, the use of biomass-based reagents is in line with the general sustainability approaches, which seek to decarbonize pharmaceutical production and eliminate reliance on non-renewable resources (Kar et al., 2021).

The use of renewable feedstocks, substitution of hazardous reagents with less hazardous ones is also one of the basic tenets of green chemistry in pharmaceutical synthesis. The conventional API production usually involves the use of toxic reagents, corrosive acids, and stoichiometric oxidants that are of great danger to human health and the environment. The strategies of safer reagent replacement aim at choosing less toxic, more selective, and easy to manipulate reagents, thus enhancing the safety of the processes and minimizing waste production. Alternative reducing agents and the use of benign oxidants and catalytic systems have led to quantifiable gains in the environmental and operational performance (Ahsan et al., 2020). Recent reports note that the reagent replacement can be most efficient when sustainability is taken into account at the initial stage of the process development, allowing the systematic removal of hazardous substances without interfering with synthetic performance (Stefanache et al., 2025).

The other important feature of green reagent design is that it encourages step-economical and protecting-group-free synthesis. Protecting-group methods, although frequently required in the construction of complex molecules, add extra reaction steps, reagents, solvents, and purification demands, all of which add to wastage and decreased efficiency. The atom economy concept emphasizes on the need to reduce unwarranted transformations and maximize on the use of the reactants in the product (Trost, 1991). Protecting-group-free methods focus on chemoselective and catalytic reactions that allow one to directly functionalize and thus minimize the number of synthetic processes and the environmental footprint. Such strategies have been found to become more and more important in API synthesis, where multiple step pathways can dramatically increase Process Mass Intensity and cost of production.

Industrially, step-economical synthesis has obvious benefits other than environmental ones. The minimization of the reaction steps makes it easier to control the processes, reduces development periods, and increases the scalability, which is important to well-developed API supply chains. The sustainability efforts in the industry have emphasized the idea that effective route design, green reagents and renewable feedstocks can provide significant savings in material consumption and waste production as well as enhance the overall process reliability (Koenig et al., 2019). This, together with the continued incorporation of renewable feedstocks, more benign reagents and economical step-wise synthesis strategies, is being considered a strategic necessity as opposed to an optional improvement.

The renewable feedstocks and green reagents play a significant role in the creation of a sustainable API production. This will force them to take a holistic approach that incorporates the molecular design, optimization of the process and industrial partnership. Such approaches will probably become one of the main characteristics of the pharmaceutical production of the next generation as regulatory frameworks and sustainability demands continue to evolve. Table 6 illustrates some of the primary renewable feedstocks and green reagent methods that have been utilised to produce API in an environmentally friendly fashion.

Table 6. Renewable feedstocks and green reagent strategies for sustainable API synthesis

Strategy	Description	Sustainability Advantage	Key References
Biomass-derived reagents	Use of renewable raw materials such as formic acid and bio-based intermediates	Reduced carbon footprint and resource depletion	Liu et al. (2015); Kar et al. (2021)

Safer reagent replacement	Substitution of toxic reagents with benign alternatives	Improved process safety and reduced waste	Ahsan et al. (2020); Stefanache et al. (2025)
Protecting-group-free synthesis	Elimination of unnecessary protection/deprotection steps	Enhanced atom economy and step efficiency	Trost (1991); Koenig et al. (2019)

5. Process Intensification and Continuous Manufacturing

The new strategies towards enhancement of sustainability in the production of Active Pharmaceutical Ingredient (API) have become continuous manufacturing and intensification of the processes. Traditionally, the production of pharmaceuticals has traditionally been based on the batch processing which is flexible but has been associated with long processing time, large volumes of solvents, ineffective heat and mass transfer and high amounts of waste generation. These restrictions do not only increase the environmental load, but are also hard to scale, reproducible and safe to operate. Comparative analysis of batch and continuous manufacturing has indicated that the nature of batch manufacturing is less efficient in terms of energy consumption and material consumption, particularly in complex multistep API syntheses (Hock et al., 2021; Rogers and Jensen, 2019).Continuous manufacturing is a paradigm shift of pharmaceutical production since it enables reactions and downstream processes to occur in a steady-state manner. The advantages of this process are an improved management of the process, reduced solvent and reagent inventory, reduced safety, and quality of the product. The continuous systems allow the correct control of reaction parameters such as temperature, residence time and mixing that can lead to higher yields and reduction of impurities formation. Continuous processing is also directly linked to the idea of waste prevention and energy efficiency in the context of green chemistry and, therefore, a significant enabler of sustainable API production (Rogers and Jensen, 2019).One of the key aspects of continuous manufacturing is flow chemistry which has been extensively talked about as a green technology in the production of API. Flow systems are operated with small channels or reactors that have improved heat and mass transfer compared to the batch reactors. This enables the application of safer reagents and exothermic reactions, minimises the amount of solvents used and energy consumed. It has been demonstrated by a significant number of studies that the flow-based synthesis can significantly reduce the Process Mass Intensity and increase the overall efficiency of the process of pharmaceutical intermediates and APIs (Ferlin et al., 2020). Also, flow chemistry allows combining multiple steps of a reaction, including telescoped processes that further reduces the wastes and purification requirements (Rogers and Jensen, 2019).Besides flow chemistry, other process intensification technologies have been developed to support continuous production of pharmaceuticals. These are advanced filtration systems, advanced separation units, and modular reactor systems that maximise throughput and reduce equipment footprint and resources. To illustrate this, modular continuous filtration technologies have enabled effective solidliquid separation in continuous mode which is one of the historical bottlenecks in the pharmaceutical production process (Steenweg et al., 2021). The technologies are applied to make API greener by decreasing the solvent consumption, downtime, and efficiency.Despite the above advantages, regulatory and implementation concerns should be closely looked into in as far as the widespread application of continuous manufacturing in the pharmaceutical sector is concerned. The regulatory frameworks were historically modelled to operate on batch processing that needed new direction to allow continuous systems. The latest regulatory experience highlights that consistent production may be entirely in line with the current quality and safety principles provided that it is accompanied by effective process management and validation plans (Ojha & Bhargava, 2022). The modern regulatory approaches also promote an increased acceptance of continuous manufacturing especially because it is consistent with the quality-by-design and sustainability goals (Alemie et al., 2025). Also, region-specific studies show that continuous manufacturing has become one of the green technologies that facilitates the application of green chemistry principles at the industrial level (Aranda-Hernandez et al., 2025).Intensification of the process and continuous manufacturing are two potent instruments of developing sustainable API synthesis. Their inclusion in pharmaceutical manufacturing systems have significant environmental, economic, and regulatory advantages, making them one of the primary forces of the future of green pharmaceutical manufacturing. Comparison of batch and continuous manufacturing methods with emphasis on the importance of process intensification in the synthesis of APIs sustainably is given in Table 7.

Table 7. Process intensification and continuous manufacturing approaches in sustainable API synthesis

Approach	Key Characteristics	Sustainability Benefits	Key References
Batch manufacturing	Flexible but resource-intensive	Higher waste and energy use	Hock et al. (2021)
Continuous manufacturing	Steady-state processing	Improved efficiency and safety	Rogers & Jensen (2019); Hock et al. (2021)
Flow chemistry	Enhanced heat and mass transfer	Reduced solvent and energy use	Ferlin et al. (2020); Rogers & Jensen (2019)

Intensified separation technologies	Modular and continuous operation	Lower solvent consumption	Steenweg et al. (2021)
Regulatory frameworks	Updated guidance for continuous systems	Facilitates industrial adoption	Ojha & Bhargava (2022); Alemie et al. (2025); Aranda-Hernandez et al. (2025)

6. Industrial Impact of Green Chemistry in API Manufacturing

The application of the principles of green chemistry in the industry has greatly influenced the manufacturing of Active Pharmaceutical Ingredient (API) and has transformed the way pharmaceutical companies design their processes, resources, and the sustainability of their processes in the long-term. Historically, the API manufacturing process has been defined by the large number of materials involved, a high level of solvents use, and the large volume of waste. Green chemistry has allowed industries to effectively deal with these challenges in a systematic way by integrating sustainability into the design of processes, scale-up, and commercial production. Consequently, green chemistry is becoming more and more popular as an environmental program, but also as a force behind operational excellence and industry competitiveness.Waste reduction is one of the most concrete industrial interests of green chemistry implementation. Historically, pharmaceutical processes have a high ratio of waste-to-product, especially when it comes to the synthesis of API with a multi-step transformation. Green metrics like the E-factor and Process Mass Intensity (PMI) have helped industries to measure waste streams and see the potential opportunities to improve. Less solvent consumption, removal of redundant operations and the use of catalytic reactions have all helped reduce E-factors and enhance material efficiency (Sheldon, 2007). Moreover, the extended use of PMI to the whole manufacturing processes with supplementary activities like cleaning of equipment has given a clearer picture of material usage, which has allowed sustaining the performance of sustainability (Benison & Payne, 2022). This has seen such developments translate to less environmental impact and an increased level of adherence to the increasingly strict environmental regulations.Green chemistry has also influenced significantly the adoption patterns of pharmaceutical industry industries other than reducing wastes. Pharmaceutical companies, particularly industry consortia have contributed to the development and best practises dissemination of green API manufacturing. The efforts are directed at the standardized measures, solvents selection manuals, and green-by-design solutions that support the informed decision-making in the industry (Koenig et al., 2019). More recently, green chemistry as a pillar of responsible API manufacturing has been emphasised in sustainability strategies that are developed by industry-led organisations, which promote transparency, innovation, and long-term environmental responsibility (Colberg et al., 2025). This type of action has led to a wider implementation of green technologies and minimization of redundancy in effort by companies.Green chemistry has a great economic and supply chain implication as well. However, contrary to the previous views that the cost of manufacturing would be higher when a company implements sustainable practices, various industrial experiences have shown that green chemistry can in many cases result in cost savings due to better yields, less usage of raw materials, and less waste disposal costs. The minimized synthetic pathways and less dependence on toxic reagents will lead to decreased development cycles and stronger production procedures (Fortunak, 2009). Besides, the supply-chain can be more resilient through the use of renewable feedstocks and reagents with lower toxicity thereby decreasing reliance on unstable or geopolitically strategic feeds. With sustainability becoming a strategic priority, green chemistry is also becoming a tool to de-risk the supply chains and enhance the long-term industrial viability (Konwarh, 2025).The concept of life cycle assessment (LCA) has become an essential resource to assess the larger environmental contribution of green chemistry programs in the manufacturing of API. LCA enables the quantitative analysis of the energy used, emission of greenhouse gases, water used and waste generated during the entire life cycle of an API, which includes the sourcing of raw materials to the finished product. The new study notes that application of LCA in designing pharmaceutical processes can provide useful insights that cannot be captured by the mass-based measures and can help industries to identify trade-offs and optimise sustainability outcomes at the system level (Chen et al., 2024). The LCA and green chemistry indicators combination helps to make decisions based on the data and make sustainability statements of the pharmaceutical manufacturers more valid.Green chemistry industrial impact on the API production is not restricted to the environmental benefits but also encompasses economic efficiency, compliance with the regulations, and strength of supply chain. With pharmaceutical industries under increasing pressure to achieve sustainability objectives and at the same time achieve reliable access to vital medicines, green chemistry presents a scientifically supported and industrially validated way forward to achieving more sustainable API manufacturing. Table 8 shows the key industrial effects of green chemistry implementation on sustainability, economics, and environmental performance during API manufacturing.

Table 8. Industrial impact of green chemistry implementation in API manufacturing

Impact Area	Key Outcomes	Industrial Significance	Key References
Waste reduction	Lower E-factor and PMI	Reduced environmental footprint	Sheldon (2007); Benison & Payne (2022)

Industry adoption	Standardized green practices	Accelerated implementation	Koenig et al. (2019); Colberg et al. (2025)
Economic performance	Cost reduction and efficiency	Improved competitiveness	Fortunak (2009); Konwarh (2025)
Life cycle assessment	System-level sustainability evaluation	Data-driven decision-making	Chen et al. (2024)

7. Challenges, Limitations, and Future Perspectives

Although there have been considerable advancements in using green chemistry methods in the synthesis of Active Pharmaceutical Ingredient (API), there are still a number of challenges and constraints that prevent the wide usage of the method in industries. Among the main barriers, there is one associated with technical feasibility and scalability. Numerous green synthetic procedures, including solvent-free reactions or mechanochemical processes, have shown encouraging performance at laboratory scale, but have problems with scale-up. Industrial translation is limited by difficulties in reaction control, heat and mass transfer, equipment compatibility and reproducibility, especially when using complicated multistep API syntheses (Jiménez-González et al., 2011). Moreover, although alternative technologies, such as mechanochemistry, have a significant positive impact on the environment, their industrial applicability and their connection to the existing pharmaceutical infrastructure are still under active research (Fantozzi et al., 2023).

Economic and infrastructure related barriers also exist which are highly influential in deciding the adoption of green chemistry in the production of API. The transformation of the well-known batch processes to the more environmentally friendly ones or the continuous systems may be costly in terms of capital investment, equipment modification, and training of the employees. Smaller manufacturers in particular may be limited by financial resources to adopt new advanced green technologies. Furthermore, the traditional manufacturing plants tend to be adapted to the traditional operations, and retrofitting may be challenging and costly to implement (Hock et al., 2021). Although green chemistry may enable long-term cost-saving, short-term implementation costs and a perceived risk of economic risk may make it slow to implement, especially in very competitive markets (Fortunak, 2009).

Another important challenge is regulatory complexity. The process of pharmaceutical production is regulated by strict regulatory systems that are aimed at controlling quality, safety, and effectiveness of the products. Although green chemistry methods are seen as more and more acceptable to the regulatory demands, their application may need further validation and documentation to show that they can be equivalent or even better than standard processes. Continuous manufacturing and new green technologies may not fit well into the current regulatory paradigm and thus may be especially difficult to navigate international regulatory requirements (Ojha & Bhargava, 2022). However, recent regulatory knowledge suggests the increasing acceptance of new manufacturing methods, as long as there is a strong quality control system and risk management system (Alemie et al., 2025).

Going forward, the developments in the area of green API synthesis should focus on technology, support of policies, and cooperation between industries. New studies are focusing on the opportunities of combining several green strategies, including biocatalysis, renewable feedstocks, and continuous processing in one, highly efficient manufacturing platform. It is expected that such holistic solutions will provide more sustainability benefits than individual process enhancements (Stefanache et al., 2025). Meanwhile, sustainability is becoming more of a strategic requirement that enhances the resilience of supply chains and the sustainability of industries in the long run (Konwarh, 2025).

Online tools and green-by-design solutions are going to have a transformational role to play in resolving the current problems. Predictive metrics, data-based route choice, and digital process modeling allow evaluating the environmental impact at an early stage, minimizing the likelihood of redesigns at a late stage. Predictive PMI calculators and similar tools can be used to make decisions and integrate sustainability into the process development at the initial stages (Borovika et al., 2019). Furthermore, the increased use of green indicators and digital sustainability models will improve transparency and comparability throughout the pharmaceutical industry and contribute to the ongoing improvement and innovation (Rose et al., 2022).

To overcome technical, economic, and regulatory hurdles and to take advantage of digitalization and collaborative models, it will be necessary to develop green chemistry in API synthesis. The rate and degree of sustainable change in pharmaceutical production will be decided by further innovation, which will be supported by the policy alignment and the commitment of the industry. Table 9 shows major challenges, limitations, and future directions that affect the adoption of green chemistry in the synthesis of API.

Table 9. Key challenges and future perspectives in green API synthesis

Aspect	Key Issues	Implications	Key References
Technical scalability	Scale-up and process control	Limits industrial translation	Jiménez-González et al. (2011); Fantozzi et al. (2023)
Economic barriers	High initial investment	Slower adoption rates	Hock et al. (2021); Fortunak (2009)

Regulatory complexity	Validation and compliance	Extended approval timelines	Ojha & Bhargava (2022); Alemie et al. (2025)
Future trends	Integrated green platforms	Enhanced sustainability	Stefanache et al. (2025); Konwarh (2025)
Digital tools	Predictive metrics and modeling	Green-by-design implementation	Borovika et al. (2019); Rose et al. (2022)

8. Conclusion

Green chemistry has become a paradigm shift in enhancing the sustainability, efficiency and stability of Active Pharmaceutical Ingredient (API) synthesis. This paper has emphasised the systematic use of the principles of green chemistry including solvent choice and catalysis to renewable feedstocks, process intensification and continuous production can significantly minimise the environmental impact of producing pharmaceuticals without compromising quality and regulatory standards. The combination of quantitative green measures, including E-factor and Process Mass Intensity, and the use of life cycle assessment tools have facilitated the assessment and optimization of API manufacturing processes at both developmental and industrial levels using data. Practical benefits of industrial use of green chemistry methods have shown as reduction in waste, increased efficiency of resources, cost savings and strengthening of supply chains. The development of more enabling technologies, biocatalysis, and digital green-by-design tools can also help facilitate the shift to more sustainable pharmaceutical production. These issues of scalability, economic investment, and regulatory complexity still affect the rate of implementation and this is the reason why there should be concerted efforts between the academia, industry and regulatory authorities. Green chemistry is not merely a business opportunity to the pharmaceutical industry but also an environmental requirement. The future of green chemistry in the provision of sustainable, efficient and responsible manufacturing of API will need further innovation that will be mediated by regulatory harmonisation and collaborative models.

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