



ISSN: 2347-6567

International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR | Vol.14 | Issue 2 | Apr - Jun - 2026

www.ijamscr.com

DOI: <https://doi.org/10.61096/ijamscr.v14.iss2.2026.636-644>

Green and Sustainable Pharmaceutical Manufacturing: Current Trends and Future Prospects

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Published on:
23.04.2026

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Futuristic
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Abstract: The pharmaceutical industry faces growing pressure to minimize its environmental footprint while maintaining high standards of quality and efficiency. Green and sustainable manufacturing has emerged as a comprehensive approach that integrates the principles of green chemistry, continuous manufacturing, solvent reduction, and energy-efficient practices to reduce waste, conserve resources, and promote safer chemical processes. This review outlines the core principles driving sustainable pharmaceutical production, including the use of safer solvents, renewable feedstocks, catalysis, biocatalysis, and green analytical techniques. It also explores the adoption of continuous manufacturing as a transformative strategy for real-time process control, scalability, and reduced environmental impact. Regulatory agencies such as the U.S. FDA and EMA are actively supporting sustainability through initiatives like Quality by Design (QbD), Process Analytical Technology (PAT), and fast-track approvals for greener technologies. Industry leaders such as Pfizer, Merck, and GlaxoSmithKline have demonstrated significant progress through case studies involving biocatalysis and solvent optimization. Despite the promise, challenges such as high initial investments, regulatory uncertainties, and technological complexity persist. Future directions point toward the integration of artificial intelligence in process optimization, circular economy models, and the expansion of bio-based pharmaceutical components. Overall, green pharmaceutical manufacturing not only addresses environmental concerns but also offers strategic advantages in process efficiency, innovation, and regulatory compliance.

Keywords: green chemistry, sustainable manufacturing, pharmaceutical industry, continuous manufacturing, biocatalysis, solvent reduction, QbD, PAT, regulatory initiatives

Introduction:

Conventional pharmaceutical production has mostly depended on batch procedures, which are costly, ecologically harmful, and contingent on hazardous chemicals and solvents. These techniques frequently result in an excessive amount of chemical waste and high energy consumption, which renders them unsustainable over time. (Constable et al., 2007).

With the global rise in environmental awareness and increasingly stringent regulatory frameworks, the pharmaceutical industry is being compelled to adopt more sustainable and eco-friendly practices. Green and sustainable manufacturing seeks to mitigate these issues by incorporating the principles of green chemistry, focusing on safer solvents, renewable feedstocks, energy-efficient processes, waste minimization, and cradle-to-grave lifecycle assessments of products. The integration of sustainability in pharmaceutical production not only addresses ecological challenges but also enhances process efficiency, reduces operational costs, and aligns with evolving regulatory and consumer expectations (Kümmerer et al., 2010; Sheldon, 2016). As the industry moves

toward a circular economy model, green manufacturing is set to become an indispensable part of pharmaceutical innovation and development (Cue, 2022).

Principles of Green Chemistry in Pharmaceuticals:

Green chemistry provides a foundation for sustainable pharmaceutical production. The 12 principles of green chemistry, first articulated by Anastas and Warner (1998), serve as a comprehensive guideline for designing safer and more efficient chemical processes. These principles aim to minimize environmental impact, enhance process efficiency, and ensure worker and consumer safety. Key principles relevant to pharmaceuticals include:

- **Prevention of waste:** It is more sustainable to prevent waste formation than to treat or clean it up after it is formed. This principle encourages optimization of synthetic routes and process design to minimize the generation of by-products (Anastas & Warner, 1998).
- **Atom economy:** Promoted by Barry Trost (1991), this principle maximizes the incorporation of all reactants into the final product, minimizing waste and improving material utilization efficiency.
- **Use of safer solvents and reaction conditions:** Traditional organic solvents, such as dichloromethane and toluene, are often hazardous and environmentally unfriendly. Replacing them with greener alternatives like water, ethanol, supercritical CO₂, or ionic liquids reduces toxicity and volatility while improving process safety and sustainability (Sheldon, 2005).
- **Energy efficiency:** Reactions should ideally occur at ambient temperature and pressure. This principle emphasizes reducing energy demands, thus lowering carbon footprints and operational costs (Constable et al., 2007).
- **Use of renewable feedstocks:** Whenever feasible, raw materials should be derived from renewable resources such as agricultural biomass instead of finite petroleum-based sources. This supports circular economy strategies and improves sustainability metrics (Clark & Deswarte, 2008).
- **Design for degradation:** Pharmaceuticals should be designed to degrade into innocuous products after use to minimize environmental persistence and toxicity in aquatic ecosystems (Kümmerer et al., 2010).
- **Catalysis:** Catalysts enhance reaction selectivity and efficiency while reducing reagent excess and by-product formation. The application of biocatalysts, in particular, allows for enantioselective transformations under mild and green conditions (Pollard & Woodley, 2007).
- **Real-time monitoring and process control:** Incorporating analytical tools such as Process Analytical Technology (PAT) enables real-time analysis and control of chemical processes, enhancing efficiency and reducing waste (Rathore & Winkle, 2009).

These principles collectively drive the transformation of pharmaceutical manufacturing into an environmentally responsible, economically viable, and socially acceptable enterprise.

Table 1: The 12 Principles of Green Chemistry (Anastas & Warner, 1998)

| Principle | Description | Relevance to Pharmaceuticals |
|--------------------------------|--------------------------------------------------|---------------------------------------|
| 1. Prevention | Avoid waste generation | Reduced chemical effluents |
| 2. Atom Economy | Maximize incorporation of reactants | Efficient synthesis of APIs |
| 3. Less Hazardous Synthesis | Use safer reagents | Lower worker exposure risks |
| 4. Designing Safer Chemicals | Minimize toxicity | Safer APIs and excipients |
| 5. Safer Solvents | Use green solvents | Replacing dichloromethane, toluene |
| 6. Energy Efficiency | Operate at ambient T/P | Reduced carbon footprint |
| 7. Renewable Feedstocks | Use bio-based inputs | Fermentation-derived APIs |
| 8. Reduce Derivatives | Avoid unnecessary steps | Less waste, shorter synthesis |
| 9. Catalysis | Use catalysts instead of stoichiometric reagents | Biocatalysis, heterogeneous catalysis |
| 10. Design for Degradation | Biodegradable products | Reduced aquatic toxicity |
| 11. Real-time Analysis | In-process monitoring | Process Analytical Technology (PAT) |
| 12. Inherently Safer Chemistry | Minimize risk of accidents | Safer reaction conditions |

Solvent Reduction and Replacement

Solvents contribute significantly to pharmaceutical waste, accounting for more than 50% of the total waste generated in typical processes. Addressing this issue is essential for greener production. Strategies for solvent reduction and replacement include:

- Solvent-free synthesis: Techniques such as mechanochemistry and solid-state reactions eliminate the need for solvents altogether. These methods not only reduce waste but also often improve reaction rates and selectivity.
- Use of green solvents: Replacing traditional solvents like dichloromethane and acetonitrile with environmentally benign alternatives is a major focus. Examples include:
 - Water: Universally available and non-toxic, often used in biocatalysis.
 - Ethanol: A renewable and low-toxicity solvent derived from biomass.
 - Supercritical CO₂: Non-flammable and recyclable, used in extraction and synthesis.
 - Ionic liquids and deep eutectic solvents: Non-volatile alternatives with tunable properties.
- Recycling and reuse of solvents: Implementing closed-loop solvent recovery systems can drastically reduce the need for fresh solvent input. Distillation, pervaporation, and membrane-based separation techniques are commonly employed.
- Solvent selection guides: Tools developed by pharmaceutical companies (e.g., Pfizer, GSK) help scientists choose solvents based on toxicity, environmental impact, and safety.

These strategies, when combined, support the transition towards cleaner, safer, and more sustainable manufacturing environments in the pharmaceutical sector.

Continuous Manufacturing

Continuous manufacturing offers greater efficiency, scalability, and control over traditional batch processes. It involves the uninterrupted production of pharmaceuticals through integrated and automated unit operations. Key benefits include:

- Reduced waste and energy use: Continuous processes are designed for efficiency, minimizing the use of raw materials and energy. Reactions are optimized to reduce solvent consumption, emissions, and by-products.
- Smaller footprint and real-time quality monitoring: Continuous systems are compact, often requiring less floor space. They facilitate on-line monitoring of critical quality attributes (CQAs) using advanced tools such as spectroscopy, enabling timely adjustments.
- Easier integration of process analytical technologies (PAT): PAT enables real-time data acquisition, allowing manufacturers to monitor, control, and optimize processes dynamically. This supports a Quality by Design (QbD) approach, improving product consistency.
- Enhanced process control and scalability: Continuous setups provide tighter control over reaction conditions (e.g., temperature, mixing), leading to better reproducibility and scalability. Scaling up is often achieved by running the system longer, rather than increasing batch size.
- Faster development cycles: Integrated design allows for rapid experimentation and optimization, accelerating time-to-market for new drugs.

Major pharmaceutical companies and regulatory bodies are increasingly supporting continuous manufacturing. The FDA has approved several drugs produced using continuous processes, and investments in this area continue to grow. As technology matures, barriers to implementation are gradually being overcome, making it a key pillar in the shift toward sustainable pharmaceutical production.

Catalysis and Biocatalysis

Catalysts are central to green chemistry, enabling more efficient, selective, and environmentally benign chemical reactions. Their use minimizes the need for excessive reagents, harsh conditions, and energy-intensive processes. Advances in catalysis and biocatalysis include:

- Use of heterogeneous and reusable catalysts: Heterogeneous catalysts, which exist in a different phase than the reactants (e.g., solid catalyst with liquid reactants), can be easily separated and reused. This minimizes waste and supports cost-effective operations. Examples include supported metal catalysts (e.g., Pd/C, Pt/Al₂O₃) used in hydrogenation reactions.
- Enzyme catalysis in aqueous media: Biocatalysts such as enzymes offer high specificity and operate under mild conditions, reducing the need for toxic solvents and high energy inputs. Enzymes are

particularly useful for chiral synthesis, an essential aspect of pharmaceutical manufacturing. The use of whole-cell biocatalysis is also gaining attention for its ability to catalyze multi-step transformations.

- Flow chemistry integration: Catalytic reactions in continuous flow systems offer enhanced control, safety, and scalability. Flow reactors improve mass and heat transfer, allow for rapid screening of conditions, and facilitate inline product purification. Flow biocatalysis, in particular, combines the benefits of enzymes with the process advantages of flow chemistry, leading to greener, faster, and more controlled syntheses.
- Advances in enzyme engineering and immobilization: Genetic engineering and protein modification techniques have enabled the creation of more robust and selective enzymes. Immobilizing enzymes on solid supports enhances their stability and reusability, making them more viable for industrial use.
- Photocatalysis and electrocatalysis: These emerging catalytic methods utilize light and electricity as sustainable energy inputs to drive reactions. They show promise for oxidation and reduction processes, enabling greener synthesis of active pharmaceutical ingredients (APIs).

Catalysis and biocatalysis not only reduce environmental impact but also open new pathways for synthetic innovation. Their continued development is key to achieving the goals of sustainable pharmaceutical manufacturing.

Green Analytical Techniques

Analytical chemistry is evolving to align with the goals of green and sustainable pharmaceutical development. Traditional analytical methods often involve hazardous reagents, large solvent volumes, and energy-intensive instrumentation. Green analytical techniques aim to minimize environmental impact while maintaining high standards of accuracy, sensitivity, and reproducibility. Key developments include:

- Miniaturization of methods: Reducing the scale of analytical procedures, such as through microextraction and micro sampling, limits the number of reagents and solvents used. Techniques like solid-phase micro extraction (SPME), microfluidic devices, and lab-on-a-chip systems are becoming increasingly popular for environmental and pharmaceutical analysis.
- Use of benign reagents: Substituting hazardous chemicals with safer alternatives contributes to a lower environmental footprint. Examples include replacing perchloric acid or chlorinated solvents with aqueous-based systems or less toxic organic solvents. Enzyme-based assays also offer a biodegradable and safe alternative for chemical detection.
- Implementation of real-time monitoring techniques: Real-time process monitoring eliminates the need for off-line analysis and allows for immediate process adjustments, reducing waste and ensuring consistent quality. Techniques such as near-infrared (NIR), Fourier-transform infrared (FTIR), and Raman spectroscopy are widely employed for in-line and at-line analysis. These tools support Process Analytical Technology (PAT) initiatives and enable Quality by Design (QbD) frameworks.
- Energy-efficient instrumentation: Advances in detector technology, portable devices, and automation have led to the development of analytical systems that consume less energy and produce less waste. LED-based detectors and miniaturized spectrometers are notable examples.
- Method simplification and green metrics: Streamlining analytical methods—reducing steps, reagents, and instrumentation—lowers environmental and operational costs. Green Analytical Procedure Index (GAPI) and Analytical Eco-Scale are tools used to evaluate and compare the greenness of analytical methods.
- Green analytical chemistry is integral to holistic sustainability in pharmaceutical manufacturing. By embracing greener analytical methods, the industry can significantly reduce its ecological footprint while improving efficiency, safety, and compliance.

Regulatory and Industry Initiatives

Regulatory bodies and industry stakeholders are increasingly recognizing the importance of sustainability in pharmaceutical manufacturing and are promoting green practices through various initiatives:

- Guidelines on Quality by Design (QbD) and Process Analytical Technology (PAT): Agencies like the U.S. FDA and EMA encourage the adoption of QbD and PAT frameworks to ensure product quality and process optimization. These approaches support environmentally friendly manufacturing by improving efficiency, reducing variability, and minimizing resource usage.
- Incentives for continuous manufacturing: Regulatory support for continuous manufacturing (CM) includes guidance documents, fast-track approvals, and technical consultations. The FDA's Emerging Technology Program and the EMA's Flexibility and Innovation in Manufacturing initiative provide a

regulatory pathway and assistance for companies transitioning to CM, which inherently supports green objectives.

- Recognition through green chemistry awards: The U.S. EPA's Green Chemistry Challenge Awards highlight groundbreaking technologies that advance green chemistry. Pharmaceutical companies have been frequent recipients for innovations such as bio catalytic syntheses, greener reaction pathways, and solvent replacement strategies.
- Sustainability standards and certifications: Organizations such as ISO and ISPE promote environmental management systems (e.g., ISO 14001) that encourage the implementation of sustainable practices in pharmaceutical manufacturing.
- Collaborative industry platforms: Initiatives like the ACS Green Chemistry Institute's Pharmaceutical Roundtable bring together leading pharmaceutical companies to collaboratively develop tools (e.g., solvent selection guides, PMI calculators), fund research, and share best practices.
- Life cycle assessments (LCA) and ESG reporting: Regulatory guidance is increasingly supportive of LCA approaches to evaluate the environmental impact of pharmaceutical products from raw material sourcing to disposal. Companies are also incorporating green chemistry principles into their ESG reporting to meet stakeholder expectations.

These regulatory and industry initiatives not only drive innovation and compliance but also create a collaborative ecosystem for advancing sustainable pharmaceutical manufacturing globally.

Case Studies

Several pharmaceutical companies have adopted green approaches, demonstrating the practical impact of sustainable practices:

- Pfizer's synthesis of sertraline using biocatalysts: Pfizer implemented an innovative bio catalytic route for synthesizing the antidepressant sertraline. This method replaced traditional stoichiometric reagents with an engineered enzyme, significantly improving yield and selectivity while reducing waste and energy consumption. The approach also minimized the use of hazardous chemicals and facilitated a greener overall process.
- Merck's greener synthesis of sitagliptin: Merck developed a highly efficient bio catalytic process for producing sitagliptin, a diabetes medication. The new process utilized a transaminase enzyme, engineered for enhanced activity and stability. Compared to the traditional chemical synthesis, the bio catalytic route led to a 19% increase in yield, a 10–13% reduction in overall waste, and elimination of heavy metals.
- GSK's Solvent Sustainability Guide: GlaxoSmithKline (GSK) created a Solvent Selection Guide to help chemists make informed decisions about solvent use. The guide ranks solvents based on health, safety, and environmental impact, promoting the use of greener alternatives. It has become a benchmark for sustainable solvent practices in the industry and is widely used in both academia and industry.

These case studies illustrate how green chemistry principles are being successfully applied to real-world pharmaceutical manufacturing, resulting in improved environmental performance, cost savings, and enhanced product quality.

Challenges and Limitations

While significant progress has been made in green and sustainable pharmaceutical manufacturing, several challenges continue to impede widespread implementation. These barriers are technical, economic, and organizational in nature, and addressing them requires coordinated efforts across multiple sectors.

1. High Upfront Investment and Technological Complexity

- Implementing green technologies—such as continuous manufacturing systems, solvent recovery units, or bio catalytic processes—often demands significant capital investment. These costs include:
- Infrastructure upgrades: Transitioning from batch to continuous manufacturing may require redesigning production lines, acquiring specialized equipment, and overhauling facility layouts.
- R&D costs: Developing greener synthetic routes or bio catalytic processes can be resource-intensive, requiring investment in research personnel, enzyme screening, catalyst development, and pilot-scale validation.

- Training and workforce development: Introducing new technologies often necessitates retraining existing staff or hiring personnel with expertise in process engineering, flow chemistry, or automation.
- Return on investment (ROI) uncertainty: Although green practices offer long-term cost savings through improved efficiency and reduced waste disposal, the initial investment can deter companies, particularly small- and medium-sized enterprises (SMEs), where short-term financial viability is critical.

This economic burden can slow the pace of adoption, especially in an industry that is heavily regulated and risk-averse.

2. Regulatory Uncertainty for Novel Processes

The pharmaceutical industry is governed by stringent regulatory frameworks designed to ensure product safety, efficacy, and quality. While these regulations are essential, they can pose challenges when applying new, untested manufacturing methods:

- Lack of precedent: Regulatory agencies may lack established guidelines or historical data for novel technologies such as continuous flow reactors or supercritical fluid extraction, leading to extended approval timelines.
- Validation requirements: Green technologies must meet the same rigorous validation standards as traditional methods. Demonstrating equivalence or superiority in terms of product quality, impurity profiles, and stability can be complex and time-consuming.
- Hesitation to alter approved processes: Modifying the manufacturing process of an already approved drug (e.g., to adopt a greener route) may trigger the need for regulatory resubmission or supplemental applications, which can delay product availability and incur additional costs.

Regulatory frameworks are gradually evolving to accommodate innovation, but the pace of change remains a bottleneck for rapid adoption of green practices.

3. Need for Interdisciplinary Collaboration

Green pharmaceutical manufacturing relies on a confluence of expertise across several domains:

- Chemistry: Organic chemists must develop greener synthetic routes, identify alternative reagents and solvents, and design processes aligned with green chemistry principles.
- Chemical engineering: Engineers are needed to design scalable, efficient, and safe continuous manufacturing systems, solvent recovery units, and PAT-enabled processes.
- Biotechnology: Expertise in biocatalysts and enzyme engineering is essential for implementing enzymatic processes in pharmaceutical synthesis.
- Regulatory science: Regulatory professionals must navigate evolving guidelines, ensure compliance, and articulate the benefits of green approaches to authorities.

In many organizations, siloed departments can hinder communication and cooperation. Bridging these gaps requires fostering a culture of collaboration, shared goals, and interdisciplinary training programs.

Moreover, partnerships between industry, academia, and regulatory agencies are essential to drive innovation, share risk, and co-develop best practices. Without coordinated collaboration, the full potential of green manufacturing remains difficult to achieve.

Future Outlook

As environmental regulations tighten and societal expectations shift towards sustainability, the pharmaceutical industry must continue evolving. Emerging technologies and innovative business models are shaping a new paradigm for green pharmaceutical manufacturing. Several promising directions are poised to transform the field further:

a. Integration of AI and Machine Learning in Green Process Development

Artificial intelligence (AI) and machine learning (ML) are becoming powerful tools in optimizing green pharmaceutical processes. These technologies can accelerate discovery, design, and optimization by:

- Predicting greener reaction pathways: ML algorithms can analyze large chemical databases to suggest synthetic routes that align with green chemistry principles, such as minimal waste, low toxicity, and renewable inputs.
- Optimizing reaction conditions: AI-driven models help fine-tune variables like temperature, solvent choice, and catalyst loading for maximum efficiency and minimal environmental impact.

- Process control and monitoring: AI integrated with Process Analytical Technology (PAT) enables real-time control of continuous manufacturing systems, reducing variability and energy consumption.
 - Lifecycle assessment and sustainability metrics: Predictive models assist in evaluating environmental impacts of manufacturing routes, allowing for data-driven decision-making.
- These technologies not only speed up development but also make sustainability a quantifiable and optimizable metric in pharmaceutical R&D.

b. Expansion of Bio-Based APIs and Excipients

The use of biologically derived active pharmaceutical ingredients (APIs) and excipients is expected to grow, contributing to greener supply chains and products:

- APIs from fermentation and biosynthesis: Advances in synthetic biology and metabolic engineering are enabling the production of complex APIs from renewable biomass using microbial systems.
- Natural excipients: Bio-based excipients (e.g., cellulose, starch, alginates) are biodegradable and less toxic, aligning with the design-for-degradation principle of green chemistry.
- Reduced reliance on petrochemicals: Shifting from petroleum-derived compounds to bio-based materials decreases the carbon footprint and enhances product sustainability.

Investment in biotechnology platforms and agricultural supply chains will be essential to scale up and standardize these materials for pharmaceutical use.

c. Development of Zero-Waste Facilities

Pharmaceutical manufacturing facilities of the future will aim to achieve zero-waste operations, leveraging design, technology, and circularity to minimize environmental impact:

- Closed-loop systems: Facilities will recycle solvents, reagents, water, and packaging materials, minimizing the need for virgin resources.
- Energy integration: Co-generation, solar panels, and smart energy management systems will reduce reliance on fossil fuels.
- Waste valorization: By-products and waste streams can be converted into useful materials such as reagents, fuels, or building blocks for other industries.
- Water neutrality: Technologies such as advanced filtration, distillation, and reuse systems will help reduce water consumption and effluent discharge.

Achieving zero waste will require comprehensive system design, policy support, and cross-sector collaboration with environmental and waste management industries.

d. Circular Economy Models in Pharmaceutical Supply Chains

The linear model of “take-make-dispose” is giving way to circular economy strategies, where materials are kept in use for as long as possible:

- Product take-back programs: Reverse logistics systems can be implemented to collect unused or expired medications for safe recycling or disposal.
- Reusable and recyclable packaging: Innovations in sustainable packaging (e.g., compostable blister packs, reusable delivery containers) help reduce environmental burden.
- Design for reuse and remanufacturing: APIs, excipients, and even entire formulations can be designed for efficient reprocessing, minimizing raw material needs.
- Extended producer responsibility (EPR): Pharmaceutical companies may take greater accountability for environmental impacts throughout the product lifecycle, from raw materials to post-consumer waste.

Circular economy principles encourage holistic thinking, considering sustainability at every stage of a product’s life, from discovery to end-of-life.

The convergence of digital technologies, biotechnology, systems engineering, and environmental science holds great promise for the future of green pharmaceutical manufacturing. As industry and regulators align toward common sustainability goals, these innovations will pave the way for a more resilient, responsible, and regenerative pharmaceutical sector.

Conclusion

Green and sustainable pharmaceutical manufacturing has transitioned from a conceptual ideal to a strategic imperative for the pharmaceutical industry. As environmental challenges mount and regulatory

landscapes evolve, embracing green chemistry principles and sustainable engineering practices is no longer optional—it is essential for long-term viability, regulatory compliance, and global stewardship.

The integration of solvent reduction techniques, continuous manufacturing, catalysis, biocatalysis, and green analytical methods has already begun to transform pharmaceutical production. These advancements not only reduce environmental impact but also enhance operational efficiency, product quality, and safety. Regulatory frameworks such as Quality by Design (QbD) and Process Analytical Technology (PAT), along with supportive industry initiatives and recognition programs, are reinforcing the shift towards greener processes.

However, despite clear progress, challenges remain. High capital costs, technological complexity, and regulatory uncertainties continue to hinder widespread implementation. Overcoming these barriers will require a multidisciplinary approach, combining innovations in chemistry, process engineering, information technology, and environmental science with proactive policy-making and cross-sector collaboration.

Looking forward, the convergence of artificial intelligence, biotechnology, and circular economy principles holds significant promise. The development of bio-based APIs, zero-waste facilities, and smart, adaptive manufacturing systems will further accelerate the transition to sustainable models. Importantly, a cultural shift toward sustainability at all organizational levels—from research labs to executive leadership—will be critical in driving lasting change.

In conclusion, green and sustainable pharmaceutical manufacturing represents a transformative opportunity to reconcile scientific advancement with environmental and societal responsibilities. With continued innovation, regulatory support, and global cooperation, the pharmaceutical industry can lead by example in building a healthier and more sustainable future.

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