

Sustainability by Design in API Manufacturing

Sustainability is a strategic imperative across the pharmaceutical industry, driven by growing regulatory needs, investor expectations, and a global push to reduce environmental impact. The life science and healthcare sector accounts for an estimated 4–5% of total global greenhouse gas emissions, making it an emissions-intensive industry. Within this footprint, API (active pharmaceutical ingredient) manufacturing alone is responsible for roughly 25% of the pharmaceutical industry's emissions, making it a critical target for decarbonization.¹

Among APIs, small molecule compounds remain the dominant class in drug development. These compounds are characterized by having a molecular mass under one kilodalton and are typically produced via chemical synthesis. Their small size allows them to pass through cell membranes and interact with intracellular targets, making them effective and versatile therapeutic agents. From 2013 to 2023, nearly 70% of all approved new molecular entities (NMEs) were small molecules, highlighting their central role in the clinical setting.²

As the pharmaceutical industry commits to a more sustainable future, companies are actively rethinking the way small molecule APIs are manufactured. This includes applying greener chemistry principles, reengineering processes, and integrating a lifecycle perspective to reduce waste, energy use, and emissions. While 50–70% of API manufacturers have

set decarbonization targets, fewer than 20% currently have actionable implementation plans, creating a significant opportunity for progress through innovation and collaboration.¹

This white paper describes our organization's initiatives to improve the sustainability of chemical manufacturing processes and how the principles of greener chemistry provide a roadmap for success.

Small Molecule API Manufacturing Gets More Sustainable

Sustainable, or “greener”, chemistry is central to minimizing the environmental impact of small molecule API manufacturing. The concept was formalized in the 1990s by Paul Anastas and John Warner, who developed the 12 Principles of Green Chemistry³, a framework that remains highly relevant today. These principles aim to prevent waste, reduce hazardous chemical synthesis, and promote the design of safer chemicals, energy efficiency, and the use of safer solvents and renewable materials, among other goals.

Implementing greener chemistry must begin early in the chemical development process. Decisions made in the lab, long before a process reaches commercial scale, can have long-lasting impacts on efficiency, safety, and sustainability. As such, our organization is embedding greener chemistry into daily operations through three foundational pillars:



Figure 1.
The twelve principles of green chemistry.

Education and Training

Building a culture of sustainability starts with continuous education and awareness. Chemists and process development teams are equipped with both theoretical knowledge and practical tools to integrate greener chemistry principles into their everyday work. Sustainability is not treated as a separate initiative, but as a core competency embedded in every stage of process development. This includes not only understanding the environmental implications of chemical choices but also the strategic value of greener processes in terms of efficiency and cost.

Smart Synthesis Design

Innovation in synthesis design is key to making API production both greener and more efficient. Advanced tools such as our proprietary Synthia™ retrosynthesis software and state-of-the-art databases allow chemists to design smart and efficient synthesis routes, streamlining development processes, reducing reaction steps, and improving atom economy.

Technologies such as continuous flow manufacturing enhance efficiency and safety in chemical processes, while in silico modeling and AI tools enhance the ability to optimize reactions before any physical experimentation occurs. These approaches accelerate development cycles and significantly reduce resource consumption and waste.

Measurement and Optimization

Robust metrics and tools are essential to evaluate and improve the environmental footprint of chemical processes. Tools such as our DOZN™ Quantitative Green Chemistry Evaluator and internal platforms

like GreenSpeed help teams assess and compare sustainability indicators, from solvent usage and energy efficiency to waste generation, across process development projects.

This data-driven approach allows teams to track progress over time, ensuring that sustainability goals are being met and there is continuous advancement towards greater efficiency and reduced environmental impact.

A common misconception is that sustainability comes at the expense of profitability. In reality, greener chemistry principles often enhance economic performance. The following examples demonstrate that sustainability and economic viability are not in conflict, but are mutually reinforcing:

- **Waste Reduction:** Minimizing waste generation and implementing solvent recycling strategies cuts down on disposal fees and raw material usage.
- **Reduce derivatives:** Avoiding unnecessary derivatization steps (e.g., protecting groups) leads to shorter synthesis pathways, reduced solvent use, and lower material and labor costs.
- **Less hazardous synthesis:** Using less hazardous solvents and reagents can reduce workplace safety risks and lower expenses tied to handling, disposal, and compliance.
- **Atom Economy:** Designing reactions that maximize the incorporation of raw materials into the final product reduces waste and boosts cost-efficiency.
- **Energy Efficiency:** Reducing the energy input required for chemical reactions can significantly lower both environmental impact and operating costs.

Tools to Enable Greater Sustainability

To support the design and development of more sustainable manufacturing processes, our organization has developed and implemented several internal tools that enable measurement and optimization of green chemistry indicators across products. GreenSpeed and DOZN™ platforms play complementary roles in helping to embed sustainability into early-stage development and beyond.

GreenSpeed: A Digital Platform for Process Sustainability Evaluation

GreenSpeed is an in-house digital tool developed to guide greener process design during research and development. The tool is specifically tailored to evaluate manufacturing processes with a significant contribution to the environmental footprint of a given chemical product, such as APIs. It provides real-time sustainability indicators to support internal decision-making, assist R&D scientists with route scouting and selection, and enhance sustainability reporting for our customers.

The tool features a streamlined, automated workflow. By linking environmental footprint data directly with electronic laboratory notebooks, GreenSpeed eliminates the need for manual data collection and delivers an instant sustainability assessment with just a few clicks. Key metrics evaluated include process mass intensity (PMI), solvent and water usage, and CO₂ emissions.

In addition to direct data integration, GreenSpeed leverages internal synthesis knowledge, reaction databases, and retrosynthesis tools to help fill raw material data gaps. The platform also incorporates features to assess waste treatment options and recycling potential, offering a holistic view of the environmental impact of a process. With accurate input and output data from documented experiments and high-quality environmental footprint datasets, scientists can conduct robust evaluations at any stage of chemical development.

DOZN™: A Quantitative Tool Based on the 12 Principles of Green Chemistry

The DOZN™ tool is the first quantitative platform in the industry to assess the relative greenness of chemicals, synthetic routes, and manufacturing processes based on the 12 Principles of Green Chemistry, which are grouped into three major categories:

- Improving resource use.
- Increasing energy efficiency.
- Minimizing human and environmental hazards.

DOZN™ provides individual scores for each category and an overall aggregate score. This enables informed decisions about how to reduce environmental impact while improving chemical efficiency and promoting sustainability. **Figure 2** shows how the DOZN™ platform is used to calculate an aggregate score for a synthesis route based on the 12 Principles of Green Chemistry.

With approximately 1,500 active users, DOZN™ is widely adopted within our organization and serves as a valuable decision-making tool in both early development and commercial settings. While DOZN™ offers a broader view of sustainability at the molecular and process level, GreenSpeed focuses more specifically on the manufacturing phase, making the two tools complementary.

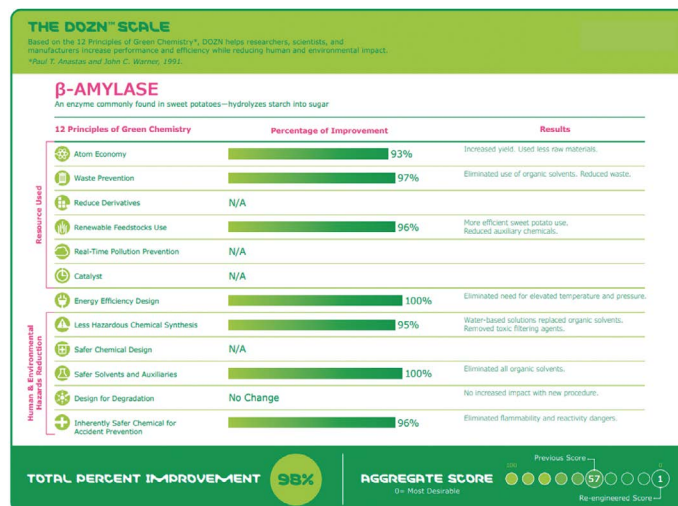


Figure 2.

DOZN™ platform aggregate score for the synthesis of β-amylase based on the 12 Principles of Green Chemistry.

Case Studies: Improving Sustainability with Synthetic Route Redesign

The following case studies demonstrate how the sustainability of a process can be significantly improved by redesigning the synthetic route.

One of the key metrics used to evaluate the sustainability of a chemical process is process mass intensity (PMI). PMI is the total mass of materials used in a process divided by the mass of the product. Cleaning solvents can sometimes be included in the calculation, but they are often excluded to focus solely on the process itself. Our GreenSpeed tool is used to facilitate PMI calculations. As described above, GreenSpeed is directly linked to electronic laboratory notebooks, allowing chemists to obtain sustainability evaluations without re-entering data. Importantly, PMI can be calculated during development, rather than waiting until the process is finalized.

GreenSpeed delivers a single PMI number and breaks the PMI down into contributing categories, such as solvent, complex materials, and water, so chemists can better understand the material intensity of each component. Complex materials include starting materials, reagents, additives, catalysts, seed crystals, and silica gel. Solvent intensity is defined as the total mass of solvent used divided by the mass of the final product; water intensity is calculated the same way. The overall PMI is the sum of solvent, water, and complex material intensity. In addition to PMI, GreenSpeed can estimate other key sustainability factors such as carbon dioxide emissions and energy consumption.

Process 1: Original vs. Redesigned Route

The original process, transferred from a client, consisted of a hydrolysis step using sodium hydroxide, followed by a disulfide exchange, and presented many opportunities for improvement. The overall yield was low, and no analytical method existed to track completion of the hydrolysis. A mass balance study revealed that the hydrolysis was incomplete and that unreacted starting material was being lost during workup.

Table 1 provides a comparison of the original and redesigned process.

In the redesigned synthetic route, the sodium hydroxide equivalent was increased, resulting in a significant improvement in final yield. One reagent in the original process required purification before use to control an impurity in the final product. However, the purification method was inefficient, with poor recovery. During development, the reagent was sourced from an alternative vendor with a low level of the critical impurity, allowing it to be used without purification.

In the original process, after the disulfide exchange step, the entire reaction mixture was concentrated to dryness and loaded onto a 40 kg silica column

for purification. This step required about 21 liters of heptane and nearly 600 liters of ethyl acetate, the equivalent of 10 drums of heptane and three drums of ethyl acetate, to produce only approximately 450 grams of product.

In contrast, the redesigned process leveraged the differing solubilities of the thiol byproduct and the desired product. The byproduct was removed via filtration before chromatography, enabling the purification to be performed with two smaller 5 kg silica columns using 120 liters of toluene and 26 liters of acetone per column. Despite dramatically reduced material use, product output was maintained at 450 g.

After chromatography, the product underwent crystallization. The original crystallization system had low yield, unpredictable crystal growth, and did not use seed crystals. The new crystallization process introduced a controlled cooling ramp and seeding, improving yield and crystal quality. The redesigned process consistently produced the desired polymorph, aligning with the client's specifications.

The product purity in the redesigned process was maintained at >99.5%, while the overall process yield improved from 39% to 66%.

Original Process	Redesigned Process	Reasoning for change/comment
Incomplete hydrolysis due to low NaOH equivalence	Increased NaOH equivalence charge and significantly increased yield	No analytical method to track hydrolysis completion, eliminated mass loss
Pre-reaction reagent purification necessary	Reagent procured from different vendor and used as received	Pre-reaction purification efficiency very low, time/resources consuming
Entire reaction residue loaded on the column	Removal of impurities by filtration prior to column chromatography	Improve column efficiency by not overloading
1-40 kg column necessary Solvent used per g starting material: 3.17 L Heptane/g 1.08 L EtOAc/g	2 smaller columns Solvent used per g starting material: 0.68 L toluene/g 0.08 L acetone/g	Studied to improve separation with different solvent systems
Low yielding crystallization system with uncontrolled crystal growth and no seeding	Controlled cooling ramp and seeding to improve crystal quality/yield	Mother liquor of the original process was a major loss of product

Table 1.

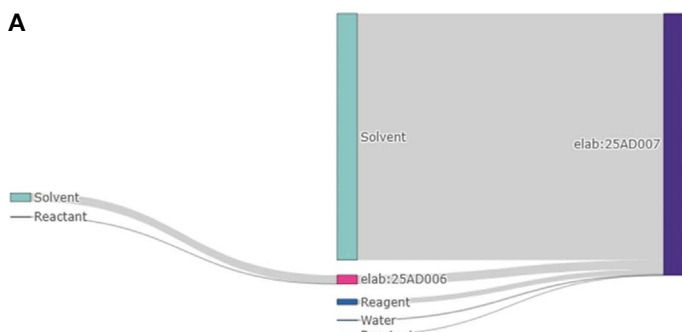
Comparison of the original and redesigned process.

Quantitative Comparison of Original and Redesigned Processes

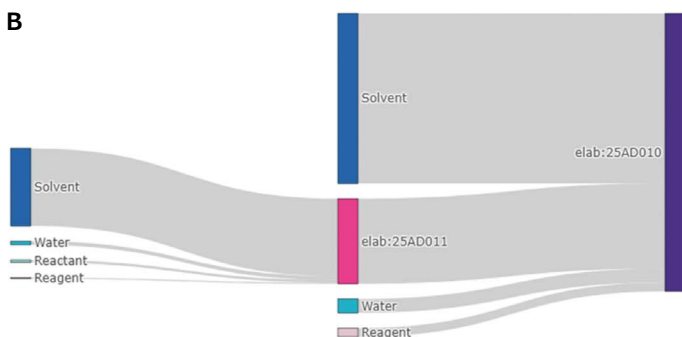
Figure 4A shows the Sankey diagram for the original process. Sankey diagrams are a type of flow diagram where the width of the connecting lines (the flow) is proportional to the quantity of flow.

The diagrams show the different process steps, with bar lengths representing reagent and solvent masses relative to others in the same process. The purple bar reflects total material usage. The PMI of the original process was 4,793.3, with solvent use as the largest contributor. For comparison, PMI values for typical multi-step small molecule processes usually fall between hundreds to low thousands, making the original process extremely inefficient.

The Sankey diagram for the redesigned process shows the input mass distribution by step (**Figure 4B**). Solvent remains the largest contributor, but the PMI dropped to 845.0, a significant reduction.



kg used/kg product	
Complex materials	104.8
Solvent intensity	4,672.6
Water intensity	15.9
PMI	4,793.3

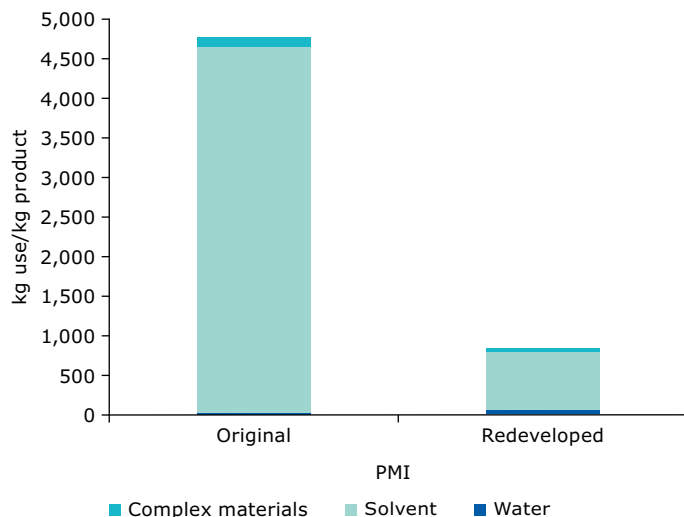


kg used/kg product	
Complex materials	38.1
Solvent intensity	753.3
Water intensity	53.6
PMI	845.0

Figure 4.

Sankey diagrams for the original process (A) and redesigned process (B).

Figure 5 compares the original and redesigned processes in terms of complex material intensity, solvent intensity, and water intensity. The most substantial reduction was in solvent intensity, which dropped from 4,672.6 to 753.3. Overall, the PMI was reduced from 4,793.3 to 845.0, demonstrating that process redesign can drive significant gains in both sustainability and efficiency.



kg used/kg product		
	Original	New
Complex materials	104.8	38.1
Solvent intensity	4,672.6	753.3
Water intensity	15.9	53.6
PMI	4,793.3	845.0

Figure 5.

Sustainability metrics for the original and redesigned processes.

Process 2: Original vs. Redesigned Route

The main starting material for Process 2 is the product from Process 1. The original three-step process included sulfonation and an amine coupling reaction. After the amine coupling step, the sulfonic acid was salted with an amine to enable purification by column chromatography. After chromatography, the sulfonic acid salt was neutralized to yield the final product as a free acid.

In the original Step 1, sulfonation was carried out using a large volume of chlorinated solvent, a reagent additive, and up to 7.5 equivalents of a corrosive acid. This acid must be added at 65 °C, posing significant safety risks to operators. In the redesigned process, a solvent screen indicated that a non-chlorinated solvent could be used, reducing the volume needed by about half.

Table 2 provides a comparison of the original and redesigned process.

Experiments showed that the reagent additive provided no benefit to product yield or quality. In fact, its presence necessitated the excessive use of corrosive acid. Eliminating the additive enabled the acid equivalent to be significantly reduced and its addition at ambient temperature before the bulk reaction was heated.

In the original process, the product of Step 1 was purified via column chromatography. The crude product from each batch had to be split into three portions for three separate columns and the purified material from all three columns would be combined for the next step. This split-column approach is necessary

due to the commercial column size availability and solvent handling limits in the production lab. Each column required approximately 300 liters of acetonitrile. In the redesigned process, column chromatography was eliminated, and crystallization was used for purification.

In the original Step 2, EDC (1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide) was used as the coupling reagent for amine synthesis. The resulting product was salted with an amine and then purified by column chromatography. As with Step 1, the crude material was divided into three portions. Each portion was purified with a 5-kg column, and each column consumes about 136 liters of acetone and 53 liters of DCM (dichloromethane).

In the improved process, EDC was replaced with DCC (dicyclohexylcarbodiimide). The urea byproduct of DCC is insoluble under the workup conditions and can be removed via simple filtration. The elimination of column chromatography was also possible in this step. The purification was achieved with a combination of crystallization and trituration.

Since column chromatography was no longer necessary, the salting of the sulfonic acid was also not necessary. As such, the entire step 3 salt neutralization step from the original process could be eliminated. The Step 2 sulfonic acid product is the final product. The elimination of the entire step removed the need for additional reagents and significantly reduced lab occupancy time. High purity was maintained throughout the process. The yield for Step 1 increased from 51% to 65%, while the combined yield for Steps 2 and 3 improved from 65% to 75%.

Original Process	Redeveloped Process	Reasoning for change/comment
High volume chlorinated solvent used	Replaced with lower volume of a non-chlorinated solvent	Chlorinated solvent is in the REACH substance of very high concern list
Usage of reagent as additive	Eliminated the usage	Experiment determined reagent as unnecessary and addition of it worsens impurity profile
Up to 7.5 eq. corrosive acid with respect to limiting reagent	3.0 eq. of corrosive acid	Elimination of unnecessary hazardous reagent
EDC as coupling reagent	Replaced EDC with Dicyclohexylcarbodiimide (DCC)	The DCC reaction simplifies the step 2 work up, byproduct DCU can be removed by filtration
3 × 5 kg columns for each batch (~ 300 L MeCN per column) 3 × 5 kg columns for each batch (~136 L acetone and ~53 L DCM per column)	Columns replaced with recrystallization/trituration	Columns are time/resources consuming, scale limiting
Salt breaking/HCl treatment required to produce the free acid	Free acid isolated and purified no salt breaking necessary 2 step process instead of 3	Process improvement, eliminated the unstable amine salt intermediate

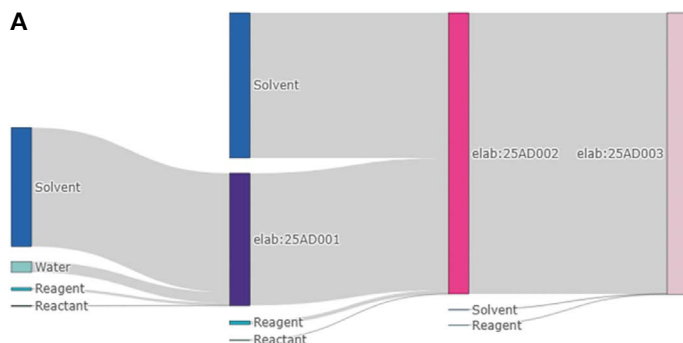
Table 2.

Comparison of the original and redesigned process.

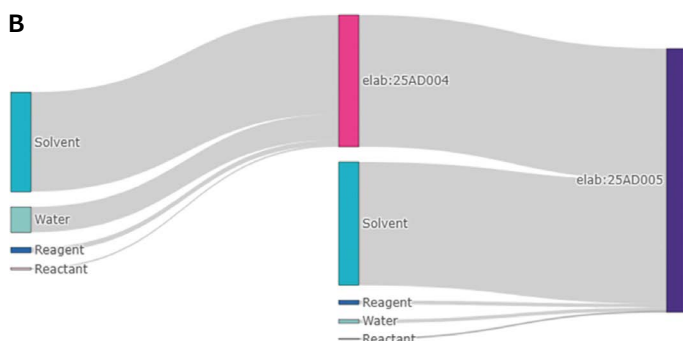
Quantitative Comparison of Original and Redesigned Processes

The Sankey diagrams for the original process showed significant solvent usage across all three steps (Figure 6A). In Steps 1 and 2, the large solvent bars reflect the high volume required for six total columns. The overall PMI for the original process was approximately 12,000, which is extremely high for a three-step small molecule synthesis.

In the redesigned process, the number of steps was reduced from three to two. The Sankey diagram of the new process reflects significantly lower solvent input, with an overall PMI of about 181.0 (Figure 6B).



kg used/kg product	
Complex materials	288.3
Solvent intensity	11,589.1
Water intensity	462.1
PMI	12,339.5



kg used/kg product	
Complex materials	8.1
Solvent intensity	152.9
Water intensity	20.0
PMI	181.0

Figure 6.

Sankey diagrams for the original process (A) and redesigned process (B).

By eliminating six 5-kg chromatography columns, solvent intensity alone dropped from 11,589.1 to 152.9. Complex material and water usage were also substantially reduced. Overall, PMI decreased by two orders of magnitude (Figure 7).

These improvements demonstrate how process redesign can dramatically improve the sustainability of API manufacturing.

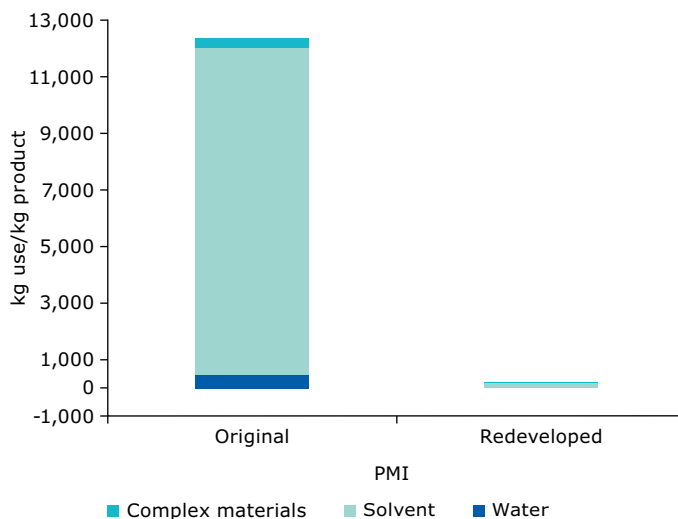


Figure 7.

Sustainability metrics for the original and redesigned processes.

Driving Sustainability Through Continuous Flow Process Intensification

Continuous flow manufacturing presents a powerful opportunity to improve process sustainability through the use of advanced reactor technologies such as plug flow reactors and continuous stirred-tank reactors. These technologies enable process intensification by addressing common challenges, such as long reaction times, high impurity levels, and operator-dependent procedures, through engineering innovation and precise control.

As an example, one of the processes targeted for improvement exhibited several of these issues. To manage the heat generated during the reaction, operators had to run extended batch reactions. However, these longer reaction times led to the formation of significant impurities, which in turn required multiple recrystallization steps to meet product specifications. Additionally, dosing operations were labor-intensive and required constant operator supervision.

By revisiting the reaction parameters, critical factors contributing to the impurity profile and inefficiencies were identified. The process was transitioned to a microreactor setup, which enabled it to be safely operated at higher temperatures while improving heat transfer. This allowed for a significant reduction in reaction time and impurity formation. The revised process also included segmented feeding of reagents into a tubular reactor, followed by in-line crystallization and filtration. This approach leveraged the heat exchange properties of the reactor to dissipate the exothermic energy more efficiently and enabled telescoping of multiple reaction steps, ultimately reducing solvent and volume requirements.

Further improvements were achieved by optimizing reagent ratios, which enhanced impurity control and minimized the need for downstream recrystallizations. Whereas the original process required four recrystallization steps, the new process achieved high purity with just one crystallization and a single recrystallization. These changes resulted in a significant reduction in solvent usage, improved material efficiency, and decreased operator intervention. Key downstream steps were also automated, including the crystallizer and filter dryer, allowing the system to handle multiple batches with minimal oversight.

Collectively, these enhancements reduced total process time from 250 to 110 hours and lowered equipment volume requirements from 300 to 100 liters. The process footprint remained the same, with all unit operations, including the pumps, tubular reactor, crystallizer, and filter dryer, integrated into the existing hood space. Most notably, a GreenSpeed assessment indicated a 20% reduction in the carbon footprint compared to the original process.

A second process improvement effort focused on modernizing an older, legacy synthesis route that had been transferred into our facility. This process, which relied on outdated analytical methods and batch technologies, faced similar challenges including long reaction times, heat management issues, and labor-intensive hot material transfers. A key problem stemmed from the use of a reagent in extreme excess, necessitating multiple recrystallizations to remove residual material.

The process was fully overhauled to address these issues. Chemically, the synthesis was redesigned as a one-pot reaction by eliminating the need for hot transfers and replacing them with a rapid-chilling heat exchanger system. This reduced operator exposure, increased safety, and brought the process under tighter control. From an engineering perspective, reagent ratios were modified to eliminate excesses, which removed the need for repeated purification steps.

By integrating flow elements such as pre-heaters and post-chillers and optimizing both the chemistry and unit operations, the process was consolidated into a streamlined two-step sequence. The result was a safer, more sustainable system with dramatically reduced solvent usage and processing time. Solvent volumes dropped from several hundred kilograms to under 100 kilograms, and total process time was shortened from nearly 400 hours to approximately 250 hours. The carbon footprint of the process was reduced by 85%.

These case studies demonstrate that engineering and chemical improvements that streamline operations, improve yields, and reduce waste almost always support sustainability goals as well. Cleaner reactions require less downstream processing, lower solvent and reagent inputs, and ultimately enable greener, more cost-effective manufacturing. In both of these examples, changes to the process enhanced sustainability metrics and yielded scalable, economically favorable, and operator-friendly processes ready for broader implementation.

Conclusion:

A More Sustainable Future for Small Molecule API Manufacturing

By applying green chemistry principles and advanced engineering approaches, such as continuous flow processing, API manufacturers can address inefficiencies, improve safety, and reduce environmental impact.

The case studies presented in this white paper highlight how process redesign at both the chemical and equipment levels can deliver measurable benefits, including reduced solvent and energy use, fewer purification steps, improved yields, and faster, more operator-friendly workflows. While many organizations have set ambitious sustainability goals, fewer have actionable implementation plans. These examples demonstrate that practical, scalable solutions exist today, and that sustainability, when rooted in scientific and operational rigor, can be aligned with both improved performance and cost-effectiveness.

References

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