ASYMCHEM

It Hasn't Been Easy For Pharma To Be Green.

CDMOs At The Forefront of Green Chemistry Are Helping To Change That.

The pharmaceutical industry is under intense pressure to reduce the environmental harm caused by drug development and manufacturing. Many companies have created new mandates for greener, more sustainable processes internally, and have extended those mandates to their CDMO partners. A few of these CDMOs are now at the forefront of green chemistry, applying its principles to reduce the environmental and human impact of pharmaceutical production.

Biotech companies need to think green as well. Most of the drugs coming to market today are acquired by large or mid-size pharma companies from small biotech companies. Partnering with a CDMO proficient in green chemistry and manufacturing can help a biotech create the most attractive drug package – one that includes a proven commercialization process minimizing toxic waste that pose safety concerns or require costly remediation.

Additional good news?

Green chemistry offers other intrinsic benefits such as greater safety, higher yields, and quicker workup and cycle times that can improve the bottom-line costs of drug commercialization.

Introduction

There's always been an uneasy reality behind the drug industry's rigorous protocols and regulations:, drug manufacturing generates more chemical waste and by-products per unit of end product than any other sector of the chemical industry.

The traditional manufacture of drugs produces several times more waste and by-products per kilogram of product than the manufacture of petrochemicals, bulk chemicals or polymers, and 80% of that waste is solvent-related. The regulatory requirements to ensure the purity and safety of complex compounds created for drug development are stringent and intensive, and consequently generate more chemical waste compared to processes for creating simpler compounds without such requirements. The more toxic and voluminous the waste, the higher the cost to treat and neutralize before releasing it back into the environment.

It makes no one happy that developing the drugs we need to cure or treat diseases, improve care and decrease suffering come at an unacceptable environmental impact or hefty financial cost. Early on, some companies attempted to sidestep the problem by outsourcing to CDMOs or CMOs based in countries with more relaxed environmental standards. But increasing pressures on multiple fronts is making change inevitable. Today, both the US and Europe require pharmaceutical companies to take responsibility for environmental impacts across their entire drug development lifecycle, regardless of where the manufacturing takes place. At the same time, environmental standards have become more stringent everywhere.

A few forward-looking CDMOs with China-based manufacturing facilities anticipated this shift years ago and began intensive investment in green chemistry to make themselves more attractive to western pharma and more accountable at home. One of these was Asymchem, which was one of the first companies elected as a "Green Factory" by the Ministry of Industry and Information Technology of China. By investing heavily in flow chemistry, enzyme transformations and other new technologies to reduce toxic waste, companies like Asymchem are demonstrating that increasing profits and protecting the environment can be complementary, rather than conflicting, goals.

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Green Chemistry Arrives

In 1998, Paul Anastas and John Warner co-authored a book setting out the 12 principles that form the basis of green chemistry. Broadly defined as the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances, green chemistry allows companies to lessen the environmental impact of chemical production.

Applying these principles to the development of pharmaceutical products created unique scientific and regulatory challenges. Making meaningful improvement requires less use of toxic organic solvents, "greener" raw materials, alternative organic synthesis methods and bio-enzyme catalysis. CDMOs like Asymchem have moved beyond merely offering cost-efficient manufacturing capacity by proactively investing in R&D and technological innovation and creating integrated smart, one-stop services designed to make developing and taking a new drug to market easier, more cost-effective and "greener" than ever before.

12 PRINCIPLES OF GREEN CHEMISTRY

1. **Prevention:** Focus on prevention of waste creation rather than treatment or clean up.
2. **Atom Economy:** Maximize incorporation of process materials into the final product.
3. **Less Hazardous Chemical Syntheses:** Wherever practicable, design synthetic methods to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals:** Design chemical products to preserve efficacy of function while reducing toxicity.
5. **Safer Solvents and Auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency:** Energy requirements should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives:** Minimize or avoid unnecessary derivatization that requires additional reagents and generates waste.
9. **Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation:** Design chemical products to break down into innocuous degradation products that do not persist in the environment.
11. **Real-time analysis for Pollution Prevention:** Develop better analytical methodologies to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention:** Substances and their form used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Source: American Chemical Society 12 Principles of Green Chemistry: https://www.acs.org/content/acs/en/greenchemistry/principles/12-principles-of-green-chemistry.html

Continuous Flow Chemistry: Greener From End To End

Traditionally, chemical reactions are performed in stirred vessels that produce a batch product. In contrast, *continuous flow* means chemical reactions are performed as materials pass through a pipe or tube, or in a cascade of continuously stirred tank reactors (CSTR), rather than while materials are held in a tank.

Flow chemistry is ideally suited to the principles of green chemistry, while also offering improved safety, quality, space savings and product capacity. Since smaller quantities of material are in play at any given time, flow processes are inherently safer. Key reaction parameters such as mixing, heating and residence time are more precisely controlled, so both product quality and yield are usually improved, sometimes dramatically. Smaller reaction volumes also mean that some highly energetic reactions that would pose unacceptable risks in a large tank can be safely managed through a continuous flow process. Required volumes of solvents and reagents are similarly reduced, as is the risk of environmental exposure to reagents, and processes can be more easily scaled.

THE NUMBERS BEHIND THE COLOR GREEN

When continuous flow production methods are integrated into the manufacture of intermediates and active pharmaceutical ingredients (APIs), the results can be eye-opening improvements in cycle times and yields, with related cost reductions. A notable example is providing by comparing batch and continuous-flow process outcomes of carbapenem synthesis.

Compared to batch production of carbapenem, Asymchem's continuous flow technology:

- reduces the production cycle from 20 days to 1.5 days
- reduces process mass intensity (PMI) by 50%
- avoids the treatment of thousands of tons of waste solvents generated in rhodium recycling, with consequent reduction in energy consumption.

Of course not every pharmaceutical manufacturing process is adaptable to a continuous flow model, and not every CDMO is willing to undertake the process of determining the suitability of a synthesis process for continuous flow technology. Since green chemistry is first of all chemistry, the subject is necessarily complex, multi-faceted, and entangled: each decision along the development cycle impacts and is impacted by many others.

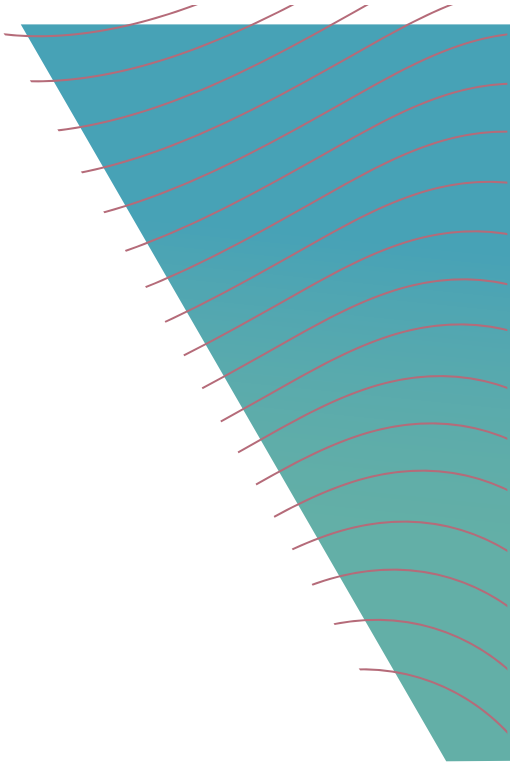
At Asymchem, the combined efforts of a multidisciplinary team are required to make that determination. This typically involves an initial proof of concept at laboratory scale to validate process parameters and characterize the desired process in detail. While process simulation and modeling are done using digital design tools, anticipated safety and environmental advantages are analyzed, as well as the robustness and reproducibility of the process. Once these steps are completed, equipment can be

The benefits of flow chemistry don't end there. Chemical reactions can be easily and rapidly analyzed, optimized and scaled, and real-time analysis provides immediate feedback on how different variables affect reaction performance. Finally, flow equipment is more modular, easier to build and to reconfigure, and generally provides substantial space savings over their batch counterparts.

CDMOs with a deep understanding of flow chemistry are able to apply the technology to a wide range of manufacturing modalities:

- Electrochemical Reaction
- Diazomethane reaction
- Dibal-H reaction
- High-temperature reaction
- Low-temperature reaction
- Curtius rearrangement reaction
- Continuous catalytic hydrogenation reaction
- Continuous reaction with high-energy reagents (TMSN3, NaN3, H2O2, TBHP, etc.)
- Ozonolysis

Bio-Enzyme Catalysis Technology: A Natural Solution.



The use of enzymes to synthesize pharmaceutical compounds is a rapidly expanding field, and for good reason: enzymes are environmentally benign, quickly and completely degraded in the environment. Enzymes are proteins that serve as catalysts for chemical reactions. In living organisms, enzymes may increase the rate of reaction by many millionfold, or even billionfold, and most enzymes function under mild or ambient biological conditions.

The use of natural or modified enzymes to synthesize drugs is known as biocatalysis. In general, biocatalytic processes are more rapid, with fewer steps, and produce less waste than traditional reaction processes, and also reduce manufacturing costs and environmental impact. Enzymes exhibit extreme selectivity: they'll usually only react with a specific substance in a specific way. That means biocatalytic reactions tend to be cleaner and safer, with fewer side-reactions that create impurities – another win since purification can be complex.

Of course the demands of pharmaceutical bio-catalytic procedures are often starkly different than those of cellular metabolism. Enzymes employed in pharmaceutical manufacturing are often subjected to higher temperatures, extremes of pH, and high concentrations of substrates, oxidants and organic co-solvents. Sometimes an enzyme must tolerate these conditions for only a few minutes or hours, but in a continuous manufacturing process, an enzyme may need to tolerate them for months. Asymchem has developed and adopted new techniques of molecular biology to create biocatalysts that are able to work efficiently in these demanding conditions, all the while keeping or even increasing their precision.

A Commitment To Bio-Enzyme Technology

While a number of CDMOs are experimenting with enzymes, a few have invested in developing a complete bio-enzyme catalysis technology platform. In Asymchem's case, this comprehensive platform covers the discovery, screening, evolutionary modification, immobilization and fermentation of new enzymes to industrial applications. By leveraging deep expertise in enzyme discovery and engineering, Asymchem has established an Enzyme Library containing more than 900 enzymes. Library stocks are maintained and replenished continually.

Many highly active engineered enzymes have been successfully used in the commercial production of statins, glitazones, penem antibiotics and other high-value compounds. As an additional advantage, many synthetic routes mediated by enzymes or cells are conducted at ambient temperature under mild reaction conditions using water as the reaction medium, reducing both process cost and risk. Access to a comprehensive bio-enzyme catalysis platform greatly increases the likelihood that any pharmaceutical development project can utilize biotransformation and enjoy its attendant benefits, including greener processes, reduced cost and supply risks and lower environmental impact.

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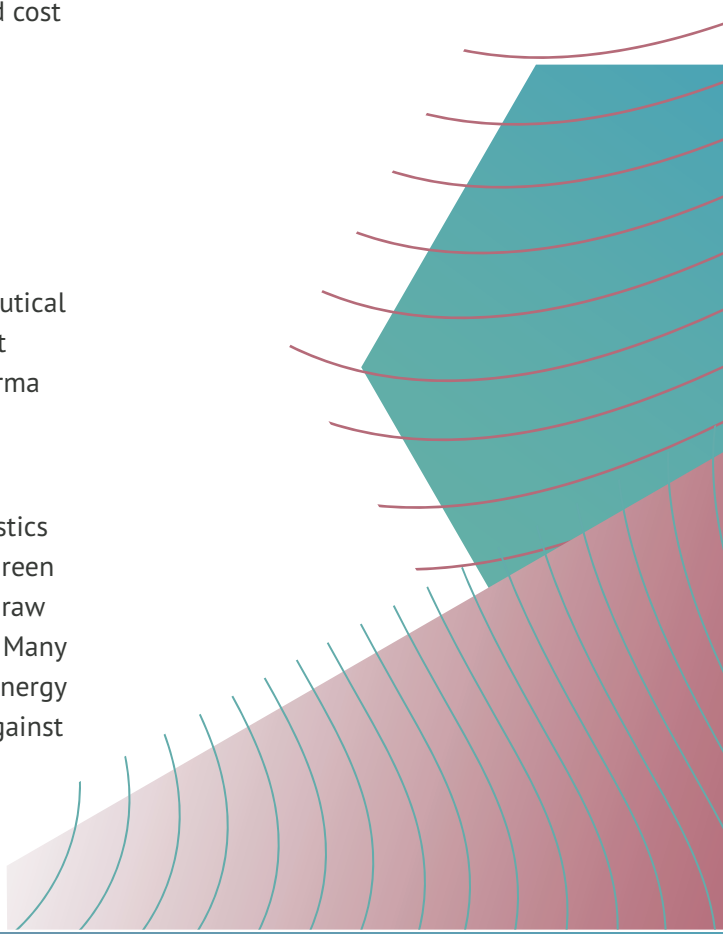
Green Is Here To Stay

As regulatory and environmental pressures mount and pharmaceutical companies increasingly require that their CDMO partners support their sustainability efforts, we can expect to see more of the pharma outsourcing industry invest in green chemistry.

Risks related to geopolitical instability such as trade disputes, politicization of supply lines, and disruption of shipping and logistics by problems such as pandemics further strengthen the case for green manufacturing. Some green methods use more easily obtainable raw materials that don't stress supply lines and lower regulatory risk. Many reduce the "embedded energy" in the final product – that is, the energy required to create a dose of medication, helping insulate costs against market price and supply fluctuations in oil.



About Asymchem

Today Asymchem is a leading contract manufacturer comprising eight manufacturing facilities in China and a fully staffed U.S. operations center in Research Triangle Park, North Carolina. Our staff of 4,500 employees include more than 1,800 scientists engaged in innovative research and process development from preclinical research to commercialization for both non GMP or cGMP products.

Asymchem has partnered with more than 400 clients across the globe, and is currently involved in more than 600 ongoing clinical projects and 30 commercial projects. We have consistently demonstrated an ability to meet project deadlines and achieve commercialization success, while exemplifying the long-term financial stability critical to project continuity and achievement. Our work has frequently won us "most valuable partner" and "strategic partner" recognition from major pharma and leading biotech companies.

Asymchem maintains an impeccable quality record and positive regulatory and environmental compliance history, with 30 successful USFDA, NMPA, TGA, MFDS inspections. Projects are handled at high standards of safety and environmental responsibility.