ASYMCHEM

Rapid Change Is Everywhere In Today's Pharma and Biotech Industry. Meaningful Innovation Is Not.

As the pace of change in the pharma and biotech industry continues to accelerate, companies are increasingly relying on CDMOs to help them meet complex challenges and capitalize on fast-evolving opportunities. CDMOs have responded in a variety of ways—adding specialized services via mergers and acquisition, making forays into biologics, or expanding their capabilities across the drug lifecycle.

In all of these cases, CDMOs face the challenge of integrating novel technologies—technologies that are either new to the CDMO or new to the industry—to deliver cost-effective innovation to the market. But developing and applying novel technologies can be a costly and complex undertaking. Roadblocks and setbacks are an inevitable frustration of doing something new. How a CDMO responds to the unexpected can determine the success or failure of a project.

What's Driving The Need to Innovate

When they first entered the market in the late 20th century, CDMOs were seen as a cost-efficient way to expand a pharma company's development and manufacturing capacity. At the time, the industry was focused on blockbuster drugs and generally utilized CDMOs for straightforward manufacturing or to augment in-house production. CDMOs weren't thought of as high-level strategic or technology partners, nor were they positioned to be. And none were expected to proactively develop technologies beyond the internal capabilities of their clients.

Today, the sheer number and complexity of compounds being pursued requires pharma companies to form more strategic alliances with CDMOs: Pharmaprojects® reports that in 2019, there were 16,181 drugs in R&D worldwide. That's up from 5,995 in 2001, with an average annual growth rate of nearly six percent since 2016. Today's drug development pipelines are also highly diversified and often require novel technologies and flexible facilities capable of handling various technical delivery formats. Consequently, CDMOs now play a critical role in all areas of drug development and commercialization.

In response, big pharma companies are consolidating their CDMO relationships, choosing strategic partners tasked with accelerating and streamlining development timelines across a multiplicity of projects.

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Biotechs and niche pharma companies are also leaning more heavily on CDMOs to access advanced technologies, equipment and deep specialization. The number of companies with only one or two drugs in R&D now represents nearly 20% of the industry roster. An unanticipated challenge that would be an annoying setback to a larger company can deal a fatal blow to an investor-funded project with limited capital, and CDMOs are helping these hopefuls carefully shepherd their coveted molecules out of the lab and into the commercial pipeline by anticipating and addressing those issues before they materialize.

Another significant trend in drug development has been described as a seismic shift eastward. According to Pharmaprojects®, 2019 was the first year when the next biggest producer of pharma R&D after the United States was not Canada, the UK, or an EU member country, but China. With seven percent of drug development companies now located there, and the whole of Asia comprising more than 23% of the industry, drug development across the eastern hemisphere is on the rise. Not surprisingly, CDMOs with manufacturing in China have evolved in parallel, from order fillers to innovators.

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Why A CDMO Culture of Meaningful Innovation Has Become Crucial

In the midst of all this change, the value of every new technology, process or system still hinges on how well it delivers on specific client needs in real-world application. Mergers and acquisitions may give a CDMO a new capability on paper, but consolidating diverse companies under a single brand name does nothing to ensure successful integration and technology transfer. Similarly, hiring a cadre of high-profile biomolecular chemists will only bear fruit if they are supported by the requisite infrastructure, related disciplines and ancillary skill sets to commercialize their work. Finally, companies that restrict their hardware investments to off-the-shelf solutions rather than taking on the challenge of building components and systems inhouse are necessarily limited in capabilities, and perhaps in vision.

Less visible, but more critical to success, are internal factors such as a CDMO's overall operational agility and flexibility, willingness to proactively invest and share risks, proven regulatory compliance and demonstrated expertise in strategic collaboration and partnership. A culture of innovation will make itself felt at the individual level as well in a "What's next?" forward-leaning posture among scientists and technologist driven by curiosity and the desire to break new ground.

Such a culture requires making the right investments at the right time—anticipating trends and developments rather than reacting to them. The first question a pharma or biotech might seek to answer when evaluating a CDMO is, where do they put their time, energy and money?

The Darwinian Approach to Enzymes

There's tremendous interest in using enzymes in pharmaceutical manufacturing, and for good reason. Enzymes are extremely efficient catalysts, accelerating the rate of chemical reactions by millions, even billions of times. Compared to traditional synthesis methods, catalytic synthesis can dramatically increase yield, shorten reaction times, pre-empt side reactions and resulting impurities, and avoid the need to recycle or neutralize enormous volumes of toxic solvents and other waste products.

But enzymes used in manufacturing must endure very different conditions from those found in a living cell. The process of creating efficacious, stable, long-life enzyme for catalytic reactions is a form of artificial selection not unlike Darwinian evolution: introduce mutations into enzymes, expose them to the chemical environment, and look for those with the desired effect. Those promising candidates are then used as the basis for another set of mutations, and the process is repeated.

This arduous process is why many CDMOs license commercial enzymes for use in synthesis, but very few have made the necessary investments to create their own. Creating hundreds or thousands of mutant enzymes and testing their fitness for a commercial manufacturing process is a massive and laborious undertaking, and the vast majority of the mutants will be failures. However, a small number will show remarkable effectiveness, selectivity and resilience –and if these can be reproduced in large numbers, the payoff to customers is more than worth the effort.

Asymchem has gone "all in" to create a comprehensive enzymatic technology platform, with a dedicated bio-engineering team focused on directed enzyme evolution and testing. By using computer-aided analysis and simulation software to predict key enzymatic properties, the evolutionary process can guide enzymes toward desired properties. A variety of gene-shuffling and error-prone copying techniques are used to create the mutant candidates. Once AI-assisted high-throughput screening identifies the best mutants, tens of thousands of clones can be produced each day. In addition, the system automates sample preparation and plate processing, and provides data tracking and inspection tools. Using this process, Asymchem has created a continuously expanding enzyme library of over 900 catalysts to draw from for client projects. The result is a wide selection of enzymes that generate chemical reactions in the shortest possible time, with the greatest possible yield and lowest impurities.

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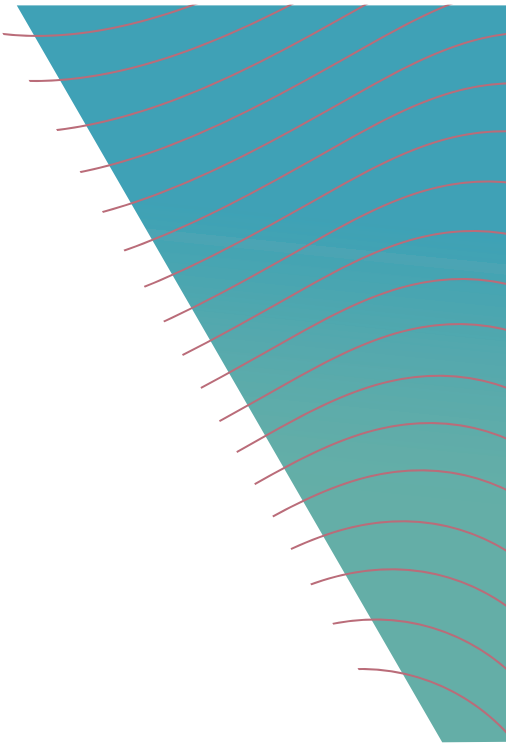
Technology Transfer: Never Drop The Baby



Stock photographers often represent this kind of handoff with runners passing a baton, but handling a baby would provide a better metaphor: it's absolutely critical that the transfer goes smoothly. Moving a process from the research and development lab to a small-scale lab, then on to manufacturing, requires careful orchestration. Ideally, the process of transferring technologies between departments or divisions should itself be organized into a structured unit to mediate exchanges between originating and receiving units and to document and verify every aspect of methods, raw materials, equipment, facilities and analytics.

At Asymchem, the departments responsible for ensuring smooth technology transfer, integration and optimization are the Project Process Development Center, Center for Early Phase Pharmaceutical Development, Center for Process Science, and the Chemical Engineering Department. Each department helps resolve the key challenges in process R&D design, optimization, scale up, production and transfer, and ensures a smooth transition from R&D to production.

A recent collaboration on a novel approach for the large-scale production of a cyclobutane derivative resulted in a 2020 paper published in Organic Process Research & Development (OPRD)1. Working with Amgen, Asymchem developed a continuous-flow process using [2 + 2] photocycloaddition of maleic anhydride and ethylene to achieve production runs delivering the target compound at throughputs exceeding 5 kg/day. Efforts to optimize the focused reaction, develop a robust isolation protocol and to design equipment and process safety required extensive cooperation between the parties and within Asymchem's various departments, including the flow group, chemical macromolecules group, and engineering department.

1 Organic Process Research & Development Article ASAP DOI: 10.1021/acs.oprd.0c00185 Copyright 2020 American Chemical Society.

Cross-Pollination: The Power of Collaboration

Almost by definition, innovation doesn't happen in isolation, but when existing ideas are combined to create something new. The larger the surface area exposed to outside ideas, the more likely meaningful innovation will occur. Scientists at CDMOs that regularly collaborate with third-party academic or commercial partners are constantly stimulated by cutting-edge research and new approaches.

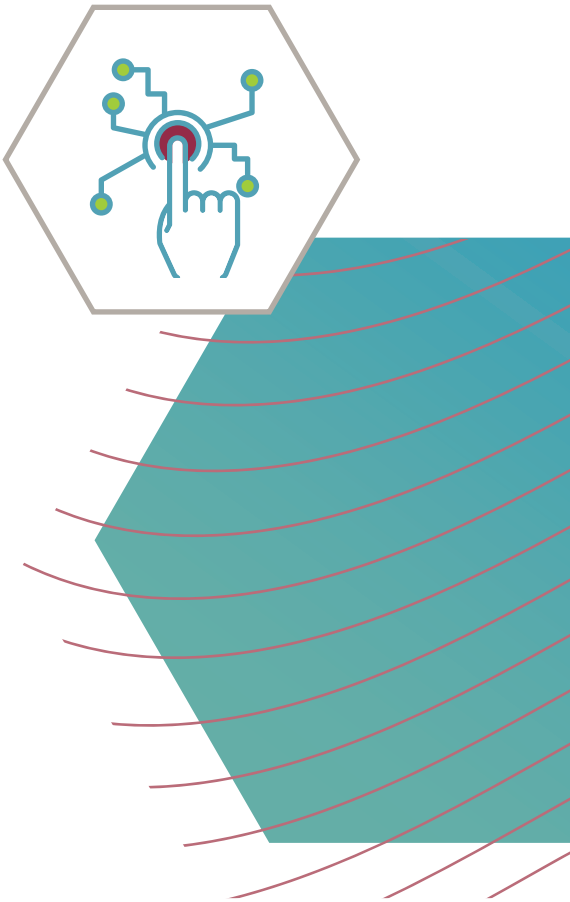
The roster of a company's science advisers can also reveal the level of their commitment to innovation. For instance, Asymchem's Scientific Advisory Board (SAB) include:

- two MacArthur Award Winners
- two members of the National Academy of Science
- An academician of the American Academy of Arts and Sciences
- two renowned chemistry professors at MIT
- leading researchers and fellows at AbbVie, BMS, Eli Lilly, and Pfizer as well as respected independent consultants

In 2014, Asymchem initiated external research collaborations with the Scripps Research Institute to develop improved, environmentally friendly process methodology. The following year, Asymchem partnered with four US-based major pharma companies for the development of more sustainable alternatives to common metal-catalyzed cross-coupling reactions.

These and other research alliances between Asymchem and major pharma have resulted in more than a dozen papers in leading journals, including *Science, Nature, the Journal of Organic Chemistry, the Journal of the American Chemical Society* and *Angewandte Chemie International Edition*. Over the last 10 years, Asymchem has been award 72 patents authorized in China and 16 international invention patents.

Innovation In The Right Hands: Securing Access



The more open a CDMO is to innovative approaches, the greater the need to protect intellectual property. These two values can coexist quite well in a single company—if the right systems and constraints are in place. Partnership, collaboration, cross-team communication and integrating multiple disciplines require a 360-degree commitment to secure intellectual property. What this looks like will vary, but best practices include:

- Secure VPN tunnels for email transfers of confidential client information.
- A Central Document Server (CDS) with assigned security access controlling access to project-specific information.
- Notebooks, production records, etc. kept locked in archive rooms under strict access control.
- Project details shared on a need-to-know basis only—process technicians never know "the big picture."
- A centralized project management system, with strict access control.
- Disabled USB port access
- Real-time monitoring of on-line behavior and alerts for suspicious behavior.
- Intrusion prevention and detection through a robust information security management platform.
- An international backup and recovery solution to ensure the redundancy and safety of archived data.

All of these measures are in place at leading CDMOs such as Asymchem. Employees, former employees and outside collaborators are all under CDAs, MSAs, and other contracts.

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-cGMP 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 a consistently demonstrated 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.