

Cover Story

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China Strides Toward Global Pharma Role

Better funded and infused with returning expatriates trained overseas, China's pharmaceutical industry is gaining strength

[Jean-François Tremblay](#)

For a country that fancies itself an emerging world power backed by thousands of years of history, China has a poor record in the pharmaceutical realm. It hasn't yet brought to market a single one of the major drugs that are sold around the world today. And China's drug industry is far better known for graft and unsafe practices than for its positive achievements.



Jean-François Tremblay/C&EN

Stepping forward With well-trained staff such as this clean-room operator at

Hengdian, Chinese companies are rapidly finding their place in the global pharmaceutical industry.

Yet, China's pharmaceutical industry is undergoing a major upgrade. Chinese who have spent decades living abroad are returning in large numbers to inject world-class practices into the country's pharmaceutical business. This strong dose of talent is complemented by spirited government efforts to build up the R&D capabilities of universities and research institutes.

"I have confidence that, in the near future, we will have some drugs 100% made in China," says Ningni Yu, the executive in charge of promoting pharmaceutical business activities in Shanghai's [Zhangjiang Hi-Tech Park](#). Yu is well-known among executives who are setting up R&D organizations in Shanghai as an effective matchmaker and troubleshooter.

"More and more companies are doing research here," Yu says. Indeed, her problem nowadays is not attracting new companies but finding space for all the firms that want to conduct R&D in Zhangjiang.

There are about 60,000 Chinese "returnees" in Shanghai alone, Yu says. They are coming to the city with foreign degrees as well as valuable work experience. Many are scientists. In China, typically, the best and brightest strive to study science, not business or law as is common in Western countries, she says.

One of the most impressive R&D facilities in Yu's technology park is being set up by [Novartis](#). The Swiss company is in the process of building and staffing a large, world-class drug discovery lab that will focus on finding ways to treat diseases that are common in China, in particular cancers caused by infection.

Novartis is not the only foreign drug company revving up R&D activities in China. Roche already operates an R&D center in Shanghai that is about half the size of what Novartis envisions, and [AstraZeneca](#) is looking to set up a big lab. As these sizable centers spring up, they are expected to familiarize researchers and business managers in China's local industry with the workings of a big-player drug company.

"China does not have a single organization that can perform all the steps involved in drug discovery," says En Li, the head of research at Novartis Institutes for BioMedical Research in Shanghai. "But the Chinese government is interested in having some of the leading Chinese institutes build their platforms and become competitive at this kind of thing."

Li is an example of the caliber of people who are heading back to China. A native of

Shanghai, he earned a Ph.D. in biology at Massachusetts Institute of Technology before spending 10 years researching and teaching at [Massachusetts General Hospital](#)'s Center for Cancer Research. Li has published more than 70 papers in peer-reviewed journals. He joined Novartis in 2003 as a senior scientist.

Another scientist who was drawn back to China is Leon Chen, now a managing partner of the venture capital firm [BioVeda China](#), also based in Zhangjiang. A fluent French speaker, Chen returned in June 2005 after spending 10 years in Belgium and 11 years in the U.S. He obtained a Ph.D. in chemistry at Catholic University of Louvain, in Louvain-la-Neuve, Belgium, and did a postdoc at MIT. As an employee at the management consulting firm McKinsey, Chen was a strategic consultant to major drug companies such as [Aventis](#) and Novartis.

China is rife with exciting chemistry research, Chen says, in both the industrial and pharmaceutical industries. He says several drug companies, not only in Shanghai but also in Beijing and in the southern city of Shenzhen, have collected animal data for promising drug candidates. A few have already filed the paperwork allowing them to begin trials on humans.

BioVeda is supporting and advising the start-up firm [NOD Pharma](#), which is testing a new diabetes treatment that delivers insulin orally instead of by injection. "A company with that kind of technology would have a market value of \$1 billion in the U.S.," Chen maintains. BioVeda is planning an initial public offering of stock for NOD with which it hopes to raise about \$100 million. NOD, Chen says, is also holding talks with major drug companies such as Eli Lilly & Co. and Novo Nordisk for foreign marketing rights.

The idea that innovative treatments are being invented in China is at odds with the global image of the country's drug industry. China sometimes seems like it is decades away from developing world-class capabilities in pharmaceuticals.

For one thing, respect for laws appears scant. Counterfeit drugs are widely sold in China, sometimes with catastrophic results. At least five people died in the southern province of Guangdong in May after they were injected with a drug made with spurious materials ([C&EN, May 22, 2006, page 11](#)).

In 2003, the Chinese drug company Hisun made the front page of the *New York Times* after its negligent safety practices led to the death of two workers. And according to the Chinese media, the former head of the [State Food & Drug Administration](#), Zheng Xiaoyu, has been detained since December for taking bribes in exchange for approving the sale of new drugs on the Chinese market.

Moreover, whereas India is home to several internationally known drug companies

such as [Ranbaxy Laboratories](#) and [Dr. Reddy's Laboratories](#), China does not have any that come close in terms of global sales, international operations, or name recognition.



Jean-François Tremblay/C&EN

By the book Two of Hengdian's plants, including the one pictured here, recently received FDA approval to export products to the U.S.

The typical Indian company's growth model is to sell generic pharmaceuticals in developed countries at premium prices and plow profits back into building international sales channels and drug discovery capabilities.

Some companies in India have several drugs in their research pipelines that already are in their second or third phase of clinical trials. Others have successfully licensed developmental drugs to big Western firms for hefty fees. Last October, for example, [Merck KGaA](#) agreed to pay Mumbai-based [Glenmark Pharmaceuticals](#) \$30 million upfront and up to \$240 million overall for a diabetes drug in Phase II clinical development.

But because few Chinese drug companies have been inspected and approved by the [U.S. Food & Drug Administration](#), only these firms can earn the high profit margins that come from exporting to the U.S. and other highly regulated markets. As a result, Chinese drug manufacturers do not generate the cash they need to expand internationally or to invest in drug discovery labs.

Bob Gatte, vice president and general manager of Grace Davison Discovery Sciences, a unit of W.R. Grace, sees opportunities in both India and China for his company's chromatography products and silica media.

In China, Grace's products usually are bought by government institutes or manufacturers of traditional medicines, whereas in India the company's customers are privately held companies making modern pharmaceuticals. "I don't see that in China

there are at the present time companies that are reaching the sophistication of a company like Ranbaxy," Gatte says.

Peter Saxon, a New Jersey-based consultant who advises drug manufacturers in China and other countries on how to comply with U.S. regulations, says it will take time before the Chinese industry amounts to much. "China's primary impact on the global pharmaceutical industry will be in the supply of low-cost advanced intermediates and active pharmaceutical ingredients," Saxon predicts. "It is possible some research group will discover a new chemical entity, but this would not be where I expect China to be a front-runner."

At major pharmaceutical trade shows, most companies from China are supplying mature, commodity-type pharmaceutical ingredients sold in large volumes. The company representatives manning the booths often exhibit scant knowledge of the dynamics of the research-based pharmaceutical industry.

"The capabilities in China are weak compared not only with the U.S., but also compared with India or Israel," acknowledges Yuwen Liu, the executive in charge of drawing investment into BioBay, a biotechnology hub that is a component of the China-Singapore Industrial Park in the eastern China city of [Suzhou](#). "But we're catching up fast," she adds.

Indeed, India is struggling to upgrade its transportation network and set up professionally managed industrial parks. China, on the other hand, boasts new airports, well-built roads, and several professionally run industrial parks. And Chinese producers of pharmaceutical ingredients are starting to realize they can boost their profit margins by becoming more sophisticated.

[Hengdian Group](#), located south of Shanghai in the province of Zhejiang, is one of China's major producers of pharmaceutical ingredients. Two of the company's six manufacturing plants were recently granted FDA approval to ship bulk pharmaceuticals to the U.S.

Xu Xiuzhong, vice president of Hengdian Group, tells C&EN that last year the company sold roughly \$375 million worth of pharmaceutical ingredients, of which about half were exported. Xu says sales are growing about 30% annually and that Pfizer recently granted Hengdian a supplier's award.

Hengdian's manufacturing capabilities are constantly improving as a result of the increased international exposure the company is receiving, Xu says. But its R&D capabilities are not well-developed yet. The company has about 50 researchers at a lab in Shanghai that opened in 2003 with room for 300 people. In the southwestern

city of Chengdu, Hengdian operates a second lab also staffed by 50 people. At both locations, Hengdian is developing generic pharmaceutical ingredients but is not engaging in drug discovery.

Hengdian's current priority, Xu says, is to better serve the needs of foreign customers who purchase such drug ingredients. Acquiring foreign distributors of generic drugs or installing drug discovery capabilities will come later. "We still have to raise our quality standards here first," he says.

At the Zhangjiang technology park, venture capitalist Chen cautions that Chinese producers of pharmaceutical ingredients are the wrong place to look for sophisticated drug discovery capabilities. Unlike in India, where it's common for producers of generic drugs to also operate drug discovery labs, innovative work in China mostly takes place at small start-up companies and at government labs.

At present, he says, about 100 truly innovative drugs are undergoing testing in China, compared with roughly 1,000 candidates in the U.S. Yet China, Chen maintains, is in many ways a better place than the U.S. to develop drugs. "Clinical trials cost less, the Chinese market is large, and development can be done faster here," he says.



Jean-François Tremblay/C&EN

Talent quest Lamottke (left) with Bicoll staff researcher Gang Lin. Lamottke hired Lin over apparently better trained candidates because he sensed Lin's aptitude for drug discovery work.

NOD Pharma, the BioVeda-supported company that is developing oral insulin, was originally based in the U.S., Chen says. And if the tests currently under way are conclusive, the treatment will be initially launched in China. Any foreign marketing will be done with the help of one or several multinational companies.

Another start-up operating in Zhangjiang is [Bicoll Biotechnology](#), a firm that studies Chinese plants as a possible source of drug leads. The company's three founding partners, one Chinese scientist and two Germans, were once students together in

Germany. Bicoll researchers extract various compounds from plants and conduct tests together with clients to discover drug leads. The company's clients, research institutes and pharmaceutical companies, conduct drug development work on the most promising leads.

Kai Lamottke, Bicoll's managing director and one of its founders, divides his time between Munich and Shanghai. This two-city lifestyle illustrates that Shanghai has become attractive not only to Chinese living abroad but also to some non-Chinese scientists with little prior knowledge of the country.

When working in Bicoll's Shanghai labs, Lamottke believes that one of his main priorities is to instill an atmosphere that is conducive to breakthrough research. "The R&D culture I bring here is from UC Berkeley," he says, referring to the University of California campus where he did research work for his master's thesis in chemistry. He also attaches a high priority to carefully selecting new employees; the best ones are not always those with the most advanced degrees, he observes.

Successful research, Lamottke says, is not the simple result of matching skills and instruments. If that were the case, inventing new drugs would be easy, he notes. It's often more important to select the right people and to provide them with a work environment in which they can be productive.



Jean-François Tremblay/C&EN

Shen

Much larger than Bicoll, the government-owned [Shanghai Institute of Materia Medica](#) also studies Chinese plants as a possible source of new treatments. SIMM's deputy director, Jinkang Shen, says the institute has a commendable record for conducting breakthrough drug discovery. Unfortunately for SIMM, the institute hasn't brought any of its discoveries to market, nor does it earn any royalties on them.

The malaria drug artemisinin was discovered at SIMM in the 1970s, Shen says. But China had poor drug development capabilities at the time and did not even have a law protecting pharmaceutical patents. Coartem, a malaria treatment based on the drug, eventually was brought to market by Novartis. Shen says SIMM also developed a

drug to treat poisoning by heavy metals that was eventually picked up by Johnson & Johnson. It's unfortunate that SIMM did not get much recognition for its work on these products, he says.

Things are changing. The institute has signed commercial agreements with two foreign companies to conduct clinical trials of new drugs invented by SIMM. One is an anti-senile dementia compound called schiperine that SIMM is codeveloping with the Swiss group Debiopharm. Although the institute is keen to further develop its drug discovery capabilities, Shen says it does not intend to become a drug company. "We see ourselves as eventually playing in China a role similar to the National Institutes of Health in the U.S.," he says.

Working in China's favor when it comes to discovery is the country's long tradition of relying on natural products to treat ailments, Shen says. These traditional medicines are a great source of drug leads. SIMM's work is also facilitated by generous government grants. "We have the material means to buy the best equipment," Shen says.



Jean-François Tremblay/C&EN

Chunlin Chen

Another sign that drug discovery capabilities are developing in China is the appearance in Shanghai of a number of cost-competitive research subcontractors. Chunlin Chen, president and chief executive officer of the contract research company [Medicilon](#), says a research dollar spent in Shanghai can stretch several times further than it would in the U.S.

His firm, a provider of chemistry and biology research services, performs work on behalf of a growing number of customers ranging from multinational companies to U.S.-based university professors. Formed in 2004, the company is growing so fast that it's constantly looking for new space in which to expand, Chen notes. It recently secured a large plot of land in Zhejiang to provide roaming space for the primates it needs for its preclinical studies.

Chen knows the steps involved in drug discovery. The holder of a Ph.D. in pharmacology and toxicology from Oklahoma State University, he worked at the U.S.

drug discovery firm [Vertex Pharmaceuticals](#) as a team leader for preclinical drug evaluation. In collaboration with other team leaders, he managed the development of an Aurora kinase inhibitor, VX-680, that Vertex eventually sold to Merck for a total of \$384 million. Another drug, the hepatitis C drug VX-350, is undergoing clinical trials. Before joining Vertex, Chen did research on drug discovery and development for six years at [Parker Hughes Institute](#) in Minneapolis-St. Paul, Minn.



Jean-François Tremblay/C&EN

Mao

While at Vertex, Chen noticed that U.S. companies were outsourcing more and more chemistry work to firms in China. But it seemed that no Chinese company was offering preclinical research services. So he and Cheney Mao, who had been his research partner at Parker Hughes, convinced Jintao Zhang, an old friend of Mao's, to set up Medicilon in Shanghai. Zhang had been director of combinatorial chemistry at the Icelandic company [DeCode Genetics](#). Headed by three partners intimately familiar with drug discovery work, Medicilon is positioned as a provider of chemistry, biology, and preclinical drug discovery services.

Medicilon's animal house—where it keeps mice, rats, dogs, and primates—is the only one permitted in Zhangjiang. Chen says companies that rely on lab animals in China are rigorously inspected by a wide range of officials. The death of primates, in particular, must be extensively explained in filed documents, he says.

Some contract research firms pursue their own independent efforts to discover new drugs. But Medicilon does not intend to go down that route, Chen says, explaining that it's clearly a conflict of interest with the client's. In preclinical studies, clients have to share sensitive information with their partners.

As at Medicilon, where the partners returned from their training and former jobs overseas, senior positions at Novartis' Shanghai research lab will be largely filled by people who are now living abroad, says Yao-chang Xu, head of chemistry at the Novartis lab. Some will be transferred internally from Novartis labs in other countries, and others will be internationally recruited.

Partly because it plans to relocate high-caliber scientists, Novartis says the cost of

operating the lab in Shanghai will be on par with that of a similar one in the U.S. or Europe.

The Novartis facility will employ between 100 and 150 scientists by the end of 2007 and is expected to reach full staffing of 500 scientists in about five years. It will be an integrated R&D facility able to perform early drug discovery and development work and to manage clinical trials. Scientists at the center will have access to all of Novartis' research data worldwide, Li says. Top-quality people, he explains, would not work there otherwise.

Novartis intends to tap into breakthrough research achieved by young biotech companies that are setting up in Shanghai and by government-funded research institutes. "We will work together on some of the research projects," Li says. "We won't just take advantage of the local resources; we want to be partners with Chinese scientists."

According to Yu, the pharmaceutical manager at the Zhangjiang technology park, no single factor can be credited for the modern pharmaceutical industry that is emerging in China. She says the return of Chinese scientists from abroad, investment in research facilities by multinational companies, and the growth of contract research companies in Shanghai all play a role.

Regulatory changes also help. She notes that China is revising its new-drug review process in order to speed up approvals. At present, she says, applications for innovative drugs are lumped together with the more numerous applications for generics.

Kevin Pan, an independent consultant, is working to initiate international clinical trials for drugs invented in China. He recently spent four years managing drug discovery chemistry and business development at Shanghai's Hutchison MediPharma, a research firm backed by foreign investors that does drug discovery work both on its own and in collaboration with Merck KGaA and Procter & Gamble. Although he returned to the U.S. for family reasons a few months ago, Pan believes that things in China are coming together nicely these days.

Until recently, China had almost no drug discovery capabilities that were up to global standards. An influx of foreign capital and foreign skills is changing that. And Chinese drug ingredient manufacturers, which are accustomed to making only generic drugs for the domestic market, are raising their production capabilities to supply a global market. The government has been increasing its support for innovative research. The booming contract research business is filling many blank areas in drug R&D. And growing professionalism in research, Pan says, is engendering increased respect for intellectual property.

Pan notes that China is projected to become the world's fifth largest market for pharmaceuticals just three years from now. "Hopefully," he says, "the Chinese pharma industry will take off and gradually become a major player in the world."

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