

China's Pharma Leaps Into Discovery

With breathtaking speed, Chinese contract research organizations have developed drug discovery services that go far beyond basic synthesis

Jean-François Tremblay

AS RECENTLY as three years ago, China's contract research industry was fledgling. A few companies were operating in Shanghai, fast-growing ones perhaps, but it didn't look as if China was destined anytime soon to become a key supplier of drug discovery and development services.



WuXi PharmaTech

Chinese Science Contract research companies are setting up modern labs in China, such as this WuXi PharmaTech facility in Shanghai, that are managed by scientists with Western experience.

Fast-forward to today, and the change is startling. Huge labs have opened or are being built in Shanghai, Beijing, Suzhou, and other places. These operations are led by world-class scientists and managers, not all of them Chinese. Several outfits offer a whole range of services, from early lead generation all the way to mass production.

China has no tradition of modern drug discovery, but the top research providers have ramped up their capabilities by attracting skilled individuals from the U.S., Japan, and other countries. A similar dynamic is unfolding in India.

"Three years ago, a lot of people were skeptical about the integrated nature of the work we were doing," says John V. Oyler, the chief executive officer of [BioDuro](#), a supplier of drug discovery and development services with integrated capabilities in chemistry and biology. Although BioDuro is based in California, the bulk of its operations are located in Beijing.

The astonishing growth of China's pharmaceutical research services companies is directly related to profound changes in the ways drugs are being discovered. Big drug companies are vigorously seeking ways to reduce the more than \$1 billion they say it costs to bring a new drug to market in the U.S. ([C&EN, June 19, 2006, page 50](#)). Although salaries have risen in recent years in China and India, the cost of outsourcing work to those countries remains lower than in developed countries.

Meanwhile, drug discovery programs in Western countries are now often propelled by small biotechnology firms that lack the infrastructure to carry out complex chemistry, toxicology, and manufacturing operations. Such companies must find these capabilities elsewhere, and China is an obvious, cost-efficient alternative.

In addition, "virtual companies" have emerged as a new type of organization pushing drug discovery programs. Taking the biotech approach to the extreme, virtual firms consist of little more than a few brilliant scientists, a promising idea, and a research budget provided by venture capitalists. Virtual firms outsource the entire drug development process to third parties.

A few years ago, there was a widespread belief that Chinese companies were unable to protect sensitive intellectual property. But Anthony D. Piscopio, chairman and CEO of the South Korean discovery research partnering firm [Chemizon](#), says intellectual property leaks in China are just a "perception." If they were truly a problem, major pharmaceutical companies including [GlaxoSmithKline](#), [Roche](#), [Novartis](#), and [AstraZeneca](#) would not be setting up R&D centers in Shanghai, he says.

As a result of these trends, Chinese contract research organizations (CROs) have moved far beyond the compound library generation work that was their bread and butter in earlier days. Today, leading Chinese CROs embark on projects that are as

challenging as those undertaken by prominent research institutes in the West.

"My preconceptions that contract research work is boring have gone out the window," says Peter N. Rehse, a structural biologist from Halifax, Nova Scotia, who joined the contract research firm [Shanghai Medicilon](#) a few months ago. "The work I do here is as interesting as what I used to do in the academic world."

Before Medicilon, Rehse was employed by [RIKEN](#), Japan's largest scientific agency, where he contributed to a major genomics project known as Protein 3000. At Medicilon, he is in charge of determining large numbers of protein structures using high-throughput techniques. "I have found that in the private sector, my projects are better funded. The food is also better," Rehse says.

Launched in 2004, Medicilon claims to be the first contract research firm in China to offer a full range of drug discovery R&D services. It can perform library synthesis; medicinal chemistry and lead optimization; process research and scale-up; structural biology; enzyme and cell assays; and in vitro and in vivo studies of the absorption, distribution, metabolism, and excretion (ADME) properties of drug candidates. The company's animal house has mice, rats, rabbits, dogs, and primates. Jintao Zhang, Medicilon's head of chemistry, estimates that the first drug to be mostly developed in China will begin human trials in the U.S. within two years.

According to Zhang, the growth of pharmaceutical outsourcing is only accelerating. To cope with the surging demand, Medicilon is building four new labs near the Pudong International Airport in Shanghai that will be large enough to accommodate 650 new employees. Zhang says the company has just issued hundreds of job offers. At present, the company employs almost 300 people.

IN THE EARLY DAYS of Chinese contract research—that's only five years ago in this industry's short life—the usual scenario was for Chinese-born entrepreneurs with Western pharmaceutical industry experience to form companies in Shanghai that provided chemistry services. They would start in a relatively small lab and move into larger premises as their business grew.



Jean-François Tremblay/C&EN

Emerging World Center

Nowadays, all sorts of contract research companies are being formed in China. They are not always located in Shanghai. They are not always focused exclusively on chemistry. They don't always start with a small lab. And the founder is not always Chinese.

The ways Chinese CROs get paid is also changing. Early on, they preferred to be paid a set fee for the services they provided. For instance, under the popular "full-time equivalent," or FTE, pricing formula, CROs quoted their customers the cost of employing their scientists on an annual basis.

The newer CROs being set up in China tend to offer a variety of pricing schemes. FTE pricing is still popular, but companies are experimenting with "risk sharing" models by which the CROs earn milestone payments when they complete certain preagreed research objectives.

Chemizon is one company that favors the risk-sharing approach. According to Piscopio, choosing the right mix of projects—those that have a higher likelihood of success and yield milestone and royalty payments—is the main business risk that Chemizon faces.

But he is relatively confident that the firm will be offered a wide enough array of projects that he and his team will be able to select some that succeed. "Research partnerships will grow because they're a pragmatic and effective way for major pharmaceutical companies to grow their pipelines while at the same time downsizing their operations," he reasons.

Despite the risk that choosing the right projects presents, Chemizon is building up its Chinese capabilities in a bold and

confident way. The firm is ramping up a 40,000-sq-ft chemistry lab on the outskirts of Beijing that will open later this year with 200 scientists. As this first facility becomes operational, the company plans to start outfitting additional labs this summer in an equally large building adjacent to the first one.

In this second facility, Chemizon will install biology labs that will provide the firm with the ability to conduct first-screening and ADME studies. Vividly illustrating the cost-effectiveness of conducting research in China, Piscopio estimates that by the end of next year, Chemizon will have spent a grand total of \$6 million to equip the two large buildings. The company is also building facilities in South Korea.

Prior industry experience is one reason Piscopio thinks he's taking a reasonably calculated risk by starting out in Beijing on a grand scale. Before launching Chemizon, he cofounded the Boulder, Colo.-based drug discovery firm [Array Biopharma](#), which he left in 2005 to pursue other interests. A New York native, he came to China for the first time in September 2005 and recalls being overwhelmed. He was surprised to discover that major cities like Shanghai and Beijing were excellent places to set up drug discovery labs.

Despite being new to China, Piscopio is not worried about Chemizon's ability to manage a large operation in the country. Several of the top managers supporting Piscopio are ethnic Chinese he knew for years in the U.S.

For instance, Yongxin Han, Chemizon's vice president of chemistry and general manager of the company's operations in China, is a graduate of the prestigious Peking University who received a Ph.D. in the U.S. and was a senior group leader at Array. He helped decide that Chemizon should set up in Beijing rather than Shanghai. "We need a lot of talented people, and Beijing is the intellectual capital of China," Han observes.

The ability to secure talented people for his firm was also a top consideration for BioDuro's Oyler. He says he was initially neutral about whether he should set up his company in Mumbai, Bangalore, Shanghai, or elsewhere. The availability of talent in Beijing tipped the balance.

"Peking University and Peking Union Medical College are in Beijing, the best toxicology expertise is in Beijing, the regulations are made in Beijing, and the National Institute of Biological Sciences is across the street from us, so Beijing is really a great location," Oyler says. Moreover, because relatively few drug discovery firms have set up in China's capital, competition for human resources is not as fierce as it is in Shanghai.

Oyler is an experienced entrepreneur who has earned tens of millions of dollars—he won't say how much exactly—by building up companies in the U.S. and selling them at high profit. He says BioDuro is a different type of company for him. It's the last one he wants to build up, and he has no intention to sell it.

One of the outfits he headed, the oncology drug firm [Genta](#), had a market value of a few million dollars when he joined in 1997, and after turning it around and hiring a new management team, it grew to a value of \$1.7 billion. He drew up the business plan for BioDuro with his old friend and business partner Masood Tayebi, who also built up and sold U.S. companies worth several billion dollars and is now BioDuro's executive chairman.

BioDuro is entirely financed by the two individuals. "There are a limited number of things I can do in my life, and I'd like to be involved in the development of a new technology that could cure a major disease," Oyler says. "That would be spectacular."

And because there are no outside investors to answer to, he says, he and Tayebi are free to run BioDuro as they please. For instance, Oyler says he would not have to justify himself to outside investors if he wanted to send 10 Chinese staff to the U.S. for training just after the company had, hypothetically, a bad quarter.

Much like Chemizon, BioDuro sees its main business as running integrated drug research programs from early-stage discovery all the way to pharmaceutical proof of concept. The company gets paid milestones when it completes projects. Oyler says he does not seek royalties on the sale of successfully launched products, nor does he want BioDuro to sponsor its own drug discovery programs. Doing so, he fears, might tempt BioDuro to assign its best people either to in-house projects or to projects that might pay the best royalties.



Jean-François Tremblay/C&EN

Big Plans BioDuro's Oyler, talking with one of the company's lab managers in Beijing, is building an integrated drug development company.

BioDuro already employs more than 300 people, and Oyler expects head count to grow to 500 by year's end. He claims to have hired the best he could find. One-third of his staff holds Ph.D.s, he says, and 10% have lived abroad. Oyler professes to have lost track of how much money he and Tayebi have spent—and are still spending—to build up BioDuro's capabilities. "We went all out," he says.

BEIJING MAY BE a great source of human resources but, like elsewhere in China, few local people have worked on drug discovery programs. To compensate, Oyler has brought in a dozen people like medicinal chemist Jon Wright, who is the company's vice president of chemistry and has 20 years of industry experience. Before joining BioDuro, Wright led a 60-person oncology drug discovery group at the New Jersey-based biopharmaceutical firm [Celgene](#) and also worked at [Pfizer](#) and [GlaxoSmithKline](#).

Another recruit is Jyun-Hung Chen, a native of Taiwan who earned a Ph.D. at [Scripps Research Institute](#) and did postdoctoral work at [Yale University](#) before joining [Ligand Pharmaceutical](#), where he conducted drug discovery for about eight years. Chen is one of BioDuro's directors of medicinal chemistry. Oyler says he's looking for six more highly experienced chemists and biologists.

China's older and more established CROs have taken note that newcomers like Medicilon, Chemizon, and BioDuro are generating enthusiastic responses from customers by offering a full range of drug discovery services.

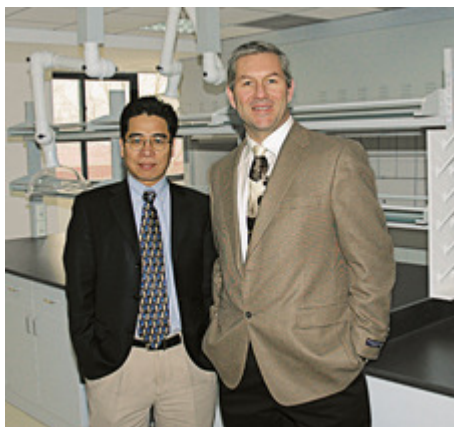
In Shanghai, ShangPharma, one of China's earliest providers of chemistry services, still conducts most of its business under the FTE pay-for-service model. The company is a holding firm that includes [ChemExplorer](#), one of the first Chinese CROs. ShangPharma's CEO, Michael Hui, says his firm has started to explore new business models involving risk sharing and strategic collaboration.

For the past two years, ShangPharma has been rapidly beefing up its range of services. Last October, the private equity firm TPG injected \$30 million into the group to help [ShangPharma](#) move forward with its diversification plans. In April 2006, ChemExplorer recruited Yajun Xu as its vice president of biology and preclinical development. A native of China, she lived in the U.S. for more than two decades.

Xu earned a Ph.D. in biochemistry at [Brandeis University](#), did postdoctoral work in cell biology at [Harvard University](#), and then entered the pharmaceutical industry. Before joining ChemExplorer, she was head of inflammation research at [Millennium Pharmaceuticals](#) in Cambridge, Mass., where she led a group of 21 researchers. There was no biology at ChemExplorer when Xu first arrived, but she now leads a group of 60. Xu hopes her team will grow to between 100 and 150 people this year.

Hui says the company is building up its biology capabilities in advance of drug company requests. "We need to be ready to offer when the customer asks for it," he says. ChemExplorer started offering biology services 10 months ago, and many customers are still testing the service. "We've hired people with lots of industry experience, but ChemPartner still needs to prove itself as an integrated drug discovery platform," Hui acknowledges.

Another area in which ShangPharma is anticipating strong business is chemistry process development and contract manufacturing. Under the leadership of Allan Hong, who joined the ShangPharma manufacturing subsidiary China Gateway Pharma Products last fall, ShangPharma is building a large-scale manufacturing facility in the Shanghai district of Fengxian that Hong says will clearly exceed the latest [U.S. Food & Drug Administration](#) requirements.



Jean-François Tremblay/C&EN

Bold Vision Chemizon's Piscopio (right) and Han visit one of the company's soon-to-open labs in Beijing.

Before joining ChemExplorer, one of Hong's jobs had been to inspect facilities in China that supplied pharmaceutical ingredients to the Swiss firm [Roche](#). Hong believes that big drug companies are progressively getting out of process development and manufacturing. "They might keep the last step in-house, but the rest will be outsourced," he says.

As the number of CROs offering a full range of services keeps growing in China, it would seem as though companies that just provide chemistry services would be a thing of the past. It is not so.

Beijing-based [Pharmaron](#) aims to become "the best chemistry service provider in the world," according to Xiaoqiang (Larry) Lou, its chief operating officer. He says the firm offers a limited range of biology services, but the bedrock of its business remains chemistry. Pharmaron claims to be particularly strong in the generation of chiral compounds, heterocyclic small molecules, and bioorganic molecules, as well as in process development. It has a small customer base of about 20 clients and says it gets its business by referrals.

Headed by Boliang Lou, Larry Lou's brother and the former director of research at Kentucky-based [CRO Advanced SynTech](#), Pharmaron opened its first lab in Beijing in 2004 with a workforce of only 20. The company now has 550 employees, of whom 470 are chemists. It is the third largest CRO in China, after [WuXi PharmaTech](#), which employs 2,700, and ChemExplorer, which now has a staff of about 1,200.

Unlike other firms, Pharmaron has not tried to load its ranks with Ph.D. holders with international experience. In the past year, however, Pharmaron has recruited several highly educated and experienced managers from the U.S. to strengthen the management of its rapidly expanding operations. Bouliang Lou, the company's chairman and CEO, says the change is needed to maintain the competitiveness of the firm. Another reason for the infusion of foreign talent is to boost Pharmaron's biology. "If we want to remain true to our aim to be the best chemistry services company, we need strong biology," he says.

One of the new recruits, Wengui Wang, now heads process development and manufacturing. Before joining Pharmaron, Wang worked for eight years at GlaxoSmithKline, where he managed projects in the area of process development and manufacturing. He holds a Ph.D. in chemistry from the [University of Montreal](#) and did postdoc work at Harvard. He is now setting up a plant for Pharmaron that will deliver kilogram quantities of pharmaceutical ingredients for use in clinical trials.

Leon Chen, a Shanghai-based venture capitalist, tells C&EN that there is room for Chinese companies that provide mainly chemistry services. He explains that although big pharma companies may have started to outsource entire drug discovery programs, they still continue to ship out smaller portions of their research activities. Chemists employed by a large drug company, he says, may outsource chemistry work when in-house resources are insufficient.

DRUGMAKERS also need the services of companies that have developed expertise in knotty areas of chemistry. For example, Chen says, it can be difficult to find a reliable supplier of pharmaceutical ingredients in kilogram quantities to use for clinical trials. Many firms claim to be able to provide such a service, he says, but the reality is that only a handful do it well.

[Brunswick Laboratories](#) is one company demonstrating that there is demand in China for contract research firms that define themselves as niche players. Unlike firms that serve the pharmaceutical industry, Brunswick's customers are manufacturers of food, beverages, cosmetics, and nutraceuticals. In December, the firm opened a lab in Suzhou, its first Asian lab to serve the region's customers.

U.S.-based Brunswick bills itself as a world leader in research and diagnostic services related to antioxidant and oxidative stress. When a food, beverage, or cosmetics manufacturer wants to advertise a new product as containing beneficial antioxidants, it goes to Brunswick to substantiate the claim.

As in the U.S., the Suzhou lab conforms to Good Laboratory Practice standards and can implement the company's patented method for measuring antioxidant capacity in food and biological systems. It serves customers in China and the rest of Asia. According to Tony Pan, the company's chief operating officer in China, as more multinational companies develop products aimed at the Asian market, business for the lab will grow.



Jean-François Tremblay/C&EN

Growing Team ChemExplorer's Hui (second from right) poses with the company's vice president of chemistry, Larry Zhang (right); Larry Hong (left); and Yajun Xu (second from left).

Positioned as a completely different type of contract research company, AbMart is focused exclusively on biological services. Headed by the entrepreneur Xun Meng, AbMart seeks to "dramatically" lower the cost of sourcing antibodies. "If we can reduce the price of producing antibodies, especially monoclonals, it will enable the generation of a standard set of antibodies for all the human proteins and for all applications," he says. Today, antibodies are too expensive to do this.

Meng says it's normal that chemistry services grew in China before biology did. "Chemistry is a more standardized discipline," he says. "Biology is more diverse, more complex." He adds that at first he found it a bit of a challenge to find biologists in China he could employ.

Meng, who used to live in Boston, where he launched a series of biotech start-ups, says it will be difficult for a single company to provide the entire range of services that the pharmaceutical industry requires. "There is room for everyone—biology services providers, chemistry services providers, and integrated firms," he says. "If you offer a good service, why wouldn't the customer come to you?"

At Pharmaron, Wang sees the growth of pharmaceutical services in China as part of a major trend. "Last century, we saw the pharmaceutical industry move from Europe to the U.S.," he says. "Now, it's perhaps moving to China and India." Mumbai, Shanghai, and Beijing are not typically thought of as the best places to go to witness the changes taking places in the ways drugs are discovered. But perhaps they are.

Chemical & Engineering News

ISSN 0009-2347

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