MADE IN CHINA?

From the outside, China may not seem an obvious place to look for a pharmaceutical breakthrough. Last year, the head of the State Food and Drug Agency was executed for taking bribes. This year, more than 80 people died in the United States alone after taking a contaminated version of the blood-thinner heparin, the main ingredient for which had been imported from China. The number of domestically discovered drugs that the Chinese pharmaceutical sector has turned into internationally successful products? Zero.

But these are desperate times. Pharmaceutical companies around the world face shrinking incomes as their leading drugs go off-patent and generics come online. The cost and complexity of new drug discovery and clinical testing is soaring and drug firms are taking a machete to their research and development (R&D) programmes.

Looked at in this light, certain features of China begin to look attractive. A spate of returnees, often with experience from Western pharmaceutical companies, has put talent on the ground. A vibrant contract research organization (CRO) industry — with more than 400 companies in Shanghai alone — allows for speedy changes of direction with minimal investment. Clinical trials can cost half or even one-fifth of what they would in the United States. The government is showing that it is serious about meeting international standards for drug development with a 6-billion renminbi (US\$900 million) investment aimed at good practices in laboratory and clinical practice (see *Nature* 455, 142; 2008). And, perhaps most importantly, multinational

companies recognize that a research branch in China helps build connections with regulatory agencies and gain access to a market that some analysts predict will be the world's second largest after the United States by 2020.

The combination of desperation outside China and promise within has convinced almost every big pharmaceutical player, including Roche, Novartis, Glaxo-SmithKline, Eli Lilly and Pfizer, to collectively invest hundreds of millions of US dollars into research operations there over the past two to three years. The

companies are somewhat cagey about how much they are investing at a time when they are laying off employees elsewhere, and when there is no guarantee of a return. But Kenneth Chien,

"You can consider what we are doing in China an experiment. We don't have to own everything."

— Tony Zhang

Jingwu Zang says his firm was attracted to China by the potential workforce and drug market.

an expert in cardiovascular medicine and an adviser to several large drug and biotechnology firms working in China, calls it "Basel on steroids", referring to the throng of pharmaceutical companies in Switzerland.

Expansion into China is an experiment, allowing companies to try out new models for seeking drugs, often relying heavily on outsourcing to CROs. "Every one is doing different things. Eventually we'll figure it out," says Li Chen, head of the Roche R&D centre in Shanghai. But there is no proven leadership, points out Mingwei Wang, director of China's National Center for Drug Screening and a pharmacologist at the Shanghai Institute of Materia Medica, the drug-research institute of the Shanghai Institutes for Biological Sciences. "Pharmaceutical companies in China have all the problems of the United States plus the lack of experience. There are no success stories, nobody has built an Amgen or Genentech in China."

Hi-tech high-rises

Most of Shanghai's pharmaceutical boom is happening in the Zhangjiang Hi-Tech Park in Pudong, east of the Huangpu river. It is in the 'new' part of Shanghai, symbolized by the Oriental Pearl Tower, with wide streets, spacious new residential complexes and golf courses. Zhangjiang boasts companies selling almost every service a pharmaceutical or biotech company could want, including the production of active ingredients, genomics, analytical and combinatorial chemistry, and preclinical toxicology testing. It is a natural place for a drug company to want to set up in.

But not GlaxoSmithKline (GSK). GSK plans to go to Puxi, the area west of the Huangpu, to build a massive permanent home for its research branch, launched in May 2007. Puxi

ILLUSTRATIONS: W. FERNANDES

GSK

GSK

has *shikumen* stone-gate dwellings and fashionable restaurants, bars, and cafes tucked into alleyways. Puxi is also home to Shanghai's, and probably China's, most prized biological sciences research institute, the Shanghai Institutes for Biological Sciences, in addition to strong research hospitals, such as the Ruijin and Zhongshan hospitals, and the medical schools of Fudan University and Jiao Tong University. "We were looking for a scientific environment," says Jingwu Zang, who heads GSK's new outpost, called R&D China. "Zhangjiang is for services. We want hard-core science."

R&D China's motto is 'Discovered in China', and it is emblazoned over an image of the Oriental Pearl Tower on the wall of the company's temporary office in Zhangjiang. Zang hopes that the phrase will replace the ubiquitous 'made in China' that brands the mostly low-margin goods made there. The unit will be the global centre for GSK's new neurodegenerative and neuroinflammatory drug-development programmes, focusing on multiple sclerosis, Parkinson's disease and Alzheimer's disease. The plan is to employ 1,000 people over the next 10 years. The company declined to give the full cost of the enterprise, but such a unit would be three to four times larger than those of other drug companies investing in the country.

GSK's decision to build such a large and permanent facility, rather than rent space as most companies do, suggests great confidence in what can be accomplished in China. It is particularly striking considering that GSK announced plans last autumn to lay off 5,000 people in other branches. Zang says that the company was drawn to China by several factors, and that cost-saving is not one of them. One attraction is the growing talent pool of scientists who trained overseas and have already returned or are willing to return. Almost half of R&D China's scientists are people who have returned from working in the United States or Europe, says Zang. Researchers are being lured back by government-supported research institutes, university positions and the opportunity to start their own government-supported businesses (see 'Started in China'). He says the company also has in mind the benefits of being able to transition drugs to the growing Chinese market more easily.

Zang rates the "overall interactive scientific environment" in Puxi as comparable to that in the Boston area of Massachusetts and hopes

Most drug firms expanding to China rent offices in the Pudong district of Shanghai.

N. ELIAS/REUTERS

to thrive in it. Over the past decade, GSK has collaborated with the Shanghai Institute of Materia Medica and it plans to do more with the Shanghai Institutes for Biological Sciences and the Shanghai Institute of Organic Chemistry.

China also offers opportunities to try an Asian angle on some intractable research problems. For example, Zang plans to investigate how multiple sclerosis differs between Asian and white populations, drawing on patients from Ruijin, Zhongshan and other hospitals. Until now, most researchers studying multiple sclerosis, such as those in the Consortium of Multiple Sclerosis Centers, of which GSK is a member, have mainly studied white people. "In the United States we hit a wall," says Zang, who was the research director of the Baylor College of Medicine Multiple Sclerosis Comprehensive Care Center in Houston, Texas, for almost 10 years. Asians seem to have a lower incidence of the disease and there is at least one clue as to why — susceptibility genes in the major histocompatibility complex sometimes differ in patients grouped by race. "We will look at the genetics very closely," he says.

Business base

Eli Lilly is also pouring millions of dollars into China — US\$100 million over the next 5 years — but it couldn't be spending it more differently. Its rented office in Zhangjiang Hi-Tech Park employs ten people, and none does scientific research. Instead, the experienced research scientists effectively figure out how to pay other companies to do drug discovery for them, focusing initially on diabetes and

oncology. They subcontract different stages of the drug-development process to Zhangjiang's myriad CROs, in which some 300 staff members are dedicated to Lilly's work. The company's China unit, which officially opened its doors on 15 October, is calling itself a "fully integrated pharmaceutical network".

"In a smaller organization, you know the bottom line much better and you know whether you made the right decision much more quickly," says Tony Zhang, head of Eli Lilly's drug-discovery unit. "You can consider what we are doing in China an experiment. We don't have to own everything." And it is an experiment he believes will work. "There is a large pool of scientific talent, vibrant entrepreneurs, and good infrastructure," he says.

A similar experiment is being planned by Pfizer. The firm already has a China Research

and Development Center that focuses on drug development and clinical trials, but it is planning to launch a similar 'virtual R&D network' that will work through partnerships with academic institutions and CROs. Such efforts by Pfizer, Roche and other companies are like "extensions of global operations," says Wang. By keeping the in-house operation small, "it's easier to open and easier to close if things don't go well".

Being able to open, close or change direction quickly is a moneysaver. Beatrijs Van Liedekerke, an associate director at Price-WaterhouseCoopers, Beijing, in charge of the business advisory group for the biotechnology, pharmaceuticals and medical-device industries, estimates that outsourcing in Chinese pharmaceutical R&D saves some 30% in costs. "They

"There are no success stories, nobody has built an Amgen or Genentech in China."

— Mingwei Wang

Started in China

While pharmaceutical companies around the world are falling over themselves to invest in China, Chinese biotech companies are struggling to be taken seriously internationally. According to Mingwei Wang, director of China's National Center for Drug Screening, the 6,600 companies in existence earlier this decade has shrunk to fewer than 3,000 after a law was implemented in 2004 requiring that drugs be made in accordance with the "good manufacturing practices" that are standard elsewhere. The remaining firms generally make generic versions of patented drugs. Just 3% of the drugs that domestic companies get approved in China each year are 'discovered in China' — and most of these are "new formulations of traditional Chinese medicine", which aren't really new, says Wang.

Now, encouraged by government support, Chinese companies are slowly gearing up towards new drugs. But the handful of true discovery companies — usually biotech firms rather than pharmaceutical companies — still gain little traction with investors, potential partners in multinational companies or the US Food and Drug Administration (FDA).

In 2002, when Qiang Yu set up Shanghai Ambrosia Pharmaceuticals with about 20 million renminbi (US\$2.5 million) from the government, "there was no drug discovery" in China, he says. "It was a blank field." Yu says he wants the first Chinese drug approved by the FDA to be his. The most promising drugs at his company are botanicals, screened from

traditional Chinese medicine libraries, which he claims work in combination to block tumour growth. "Multinationals don't want a botanical mixture. They want a single compound," says Yu. Yu is now in the second phase of fundraising but says that he is struggling to find pharmaceutical partners or investors. "Everybody is looking for later-stage products," he says. "They are demanding a

lot of data." More data might not be enough. Zensun (Shanghai) Sci & Tech, established in 2000 with 200 million renminbi (US\$30 million) from government and private sources, has taken a heart-failure drug to phase II trials at a fraction of the price it would have cost in the United States. But because the FDA sometimes doesn't accept phase II data obtained independently in China, the firm has not been able to convince potential investors of the drug's value. "When you apply to the FDA, they'll ask you to restart," says Mingdong Zhou, Zensun's chief executive. "It's a serious problem because investors evaluate us as if we were at preclinical stage, even though we are already in phase II or phase III clinical trials." **D.C.**

outsource because they don't have the expertise, they don't want to invest, or they just have too many things going on," she says. Gerald Chan, a co-founder of the Morningside, an investment company active in China, is blunter. "Drug companies had to do something to please Wall Street," he says, "and that meant outsourcing."

Roche, which in 2004 became one of the first multinationals to establish a research unit in Shanghai, is somewhere between the Eli Lilly and GSK models. Having spent some US\$70 million to \$80 million over the past four years, it now employs around 90 people in house. But it also relies heavily on CROs and partnerships with universities that, taken together, give it a total of about 250 research staff, says Chen. "You can build a drug-design chain without leaving Zhangjiang," he says.

The role of Roche's Chinese branches is partly to adapt pre-existing drugs by verifying the appropriate dose for Chinese people — essential work if the company wants to gain regulatory approval for drugs it has developed abroad. But the company also wants to make this a two-way flow, by developing a programme to identify and evaluate new drug candidates in China as far as phase II clinical trials, and pass them to Roche's global portfolio. Roche's China branch already has two cancer drugs in the preclinical stage that are ready for human trials next year. Chen agrees that outsourcing speeds up progress. "You can do several steps in parallel, and flexible resources will reduce the waiting time when

you have numerous projects with multiple compounds," he says. "By picking different CROs to do the same services in parallel, whether it's drug metabolism and pharmacokinetic studies, drug safety or oncology animal studies, pharmaceutical companies can avoid a backlog at any given point in drug development."

Wang cautions that there are limitations on just how much can be outsourced. Screening drug candidates for biological activity, for instance, requires experience that CROs are short on and this could be a concern when it comes to generating high-quality data. Very few of Zhangjiang's company's offer these types of screen. "CROs are passive. If you say 4 weeks, they'll do it. But they won't spot early

signs of deviation. It's a recipe for disaster. To interpret the data, you must be experienced."

Van Liedekerke, who has been based in China for the past two and a half years, says that China has a lot going for it, but it won't be a "deus ex machina that solves all of pharma's problems". It might solve some of them though. She gives an off-the-cuff estimate of 3–5 years before drugs discovered in China start making their way into health systems around the world. "It's just a matter of time," she says.

Drug discovery and development is becoming more complicated both scientifically and managerially, she says, and requires people with expertise in many fields to come together.

"The people that can communicate the best will win out." And whoever wins, less money will probably have been spent trying out new models in China than elsewhere.

Chan estimates that a full-time chemist in the United States costs US\$225,000 in salary and research costs per year compared with \$70,000 in China. But the price is rising quickly owing to competition and rising prices. "Shanghai used to be the most desirable spot. Now we wouldn't dare touch it," he says.

"Prices in China are going up," Chien agrees. "It will not be a bargain for much longer."

David Cyranoski is Nature's Asia Pacific correspondent.

Eli Lilly is setting up a network of subcontractors in China.