Research & duplication

China's biotech industry still lags behind when it comes to innovation. But that suits the country just fine

It was winter, and several hundred Chinese men and women were packed into a drafty hotel ballroom on the outskirts of Shanghai. Still swaddled in their brown, grey and black puffy coats, they listened as the presenter droned on in front of a too-small PowerPoint presentation. His soup of technical Chinese was punctuated by halting English phrases: "Me too," he said. "Me better."

His aim was not self-confidence building, though it was motivational speech of sorts. The speaker, a doctor and scholar at the Chinese Academy of Engineering, was lecturing a room of scientists and entrepreneurs on what many see as the most promising strategy for the Chinese biopharmaceutical industry: making copies of the biological drugs invented by scientists in developed countries (products referred to as "me-toos") and perhaps stumbling on a superior drug in the process ("me-betters").

Humans have used biological compounds in medicine for centuries – in the form of blood, organ and tissue transplants, and in vaccines – and even before that to create products like beer and bread. But only in the last few decades have biological organisms been integrated into treatments for some of the world's deadliest diseases, including diabetes, cardiovascular ailments and cancer.

Unlike chemical pharmaceuticals, which are made when elements are joined together in a process akin to cooking, biological compounds are grown. They are living organisms or their products, such as insulin, antibodies and proteins. And because they are living and mutable, they can be coaxed into adapting to specific strains of diseases and even specific patients – making medicine more personalized and effective than ever before.

Much of the production of chemical pharmaceuticals has already relocated from developed countries to India and China: Most of the world's active pharmaceutical ingredients are now made in those two countries. But developing countries have been unable to replicate more advanced biological drugs until now.

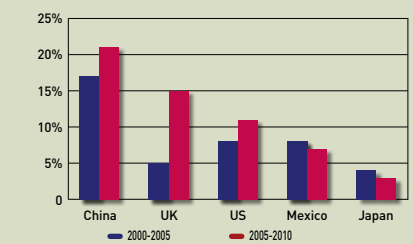
Life finds a way

Developed countries have invested heavily in biotechnology; the US has poured nearly a trillion dollars into the sector since 2000, including both the public and private sectors. So one might wonder why the US government and pharmaceutical companies have not joined forces to crack down with a fury on Chinese piracy in the biotech industry.

The truth is that making close copies of biological drugs is often perfectly legal. That's because biological drugs, like all living things, have an infinite capac-

Full speed ahead

Pharmaceutical market growth rate



Source: IMS

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ity for variation. And that makes it easy for imitators, like those gathered at the Shanghai conference, to exploit loopholes in patent laws.

"The intellectual property situation for biologics is nowhere near as clear as for chemical drugs," said Helen Chen, head of the life sciences practice at LEK Consulting and a former employee of Genentech, one of the forerunners of biotechnology in the US.

Christopher Huang, the managing director of Pharmacons, an industry services provider, concurred. "A small chemical structure is very fixed. Either you get it or you don't – you produce aspirin, then that's aspirin, and if you change it, it will be called something else. But for biological structures, even [if] the chemical composition is the same, the shape may be different. The immune impact may be different for very small tweaks of the structure," he said.

This property has allowed for a boom in the global production of "biosimilars," or biological drugs that can be shown to be "highly similar" to drugs that have already been approved for patient use. Biosimilars now meet 40-50% of global demand for biological products and account for almost all of the biological drugs produced in China.

Multinational pharmaceutical companies have been largely unable to prosecute biosimilar makers for intellectual property violations in the courts, but that hasn't stopped them from trying to waylay the industry.

Unlike the US and Europe, China lacks any notable resistance to the use of stem cells or even organized opposition to animal testing

Top-tier pharmaceutical companies have turned to lobbying for more extensive regulation on copycat products. The EU now requires biosimilars to undergo extensive clinical trials that require time and money to perform, helping to ensure that the makers of novel products preserve their lead. The US does not yet have specific regulations for biosimilars, but most speculate that similar rules will emerge soon.

But not all major pharmaceutical companies have chosen to fight against the tide of biosimilar production. "Some companies certainly have said, 'You know what, if we can't beat them, we'll join them,'" said Chen of LEK.

Merck, Boehringer Ingelheim, Samsung, and Sandoz, the generics arm of Novartis, have all unveiled plans in recent years to begin making biosimilars. Analysts at HSBC speculate that the approval of a regulatory pathway for biosimilars in the US could spur companies like Pfizer, AstraZeneca and Johnson & Johnson to make similar commitments.

Going the distance

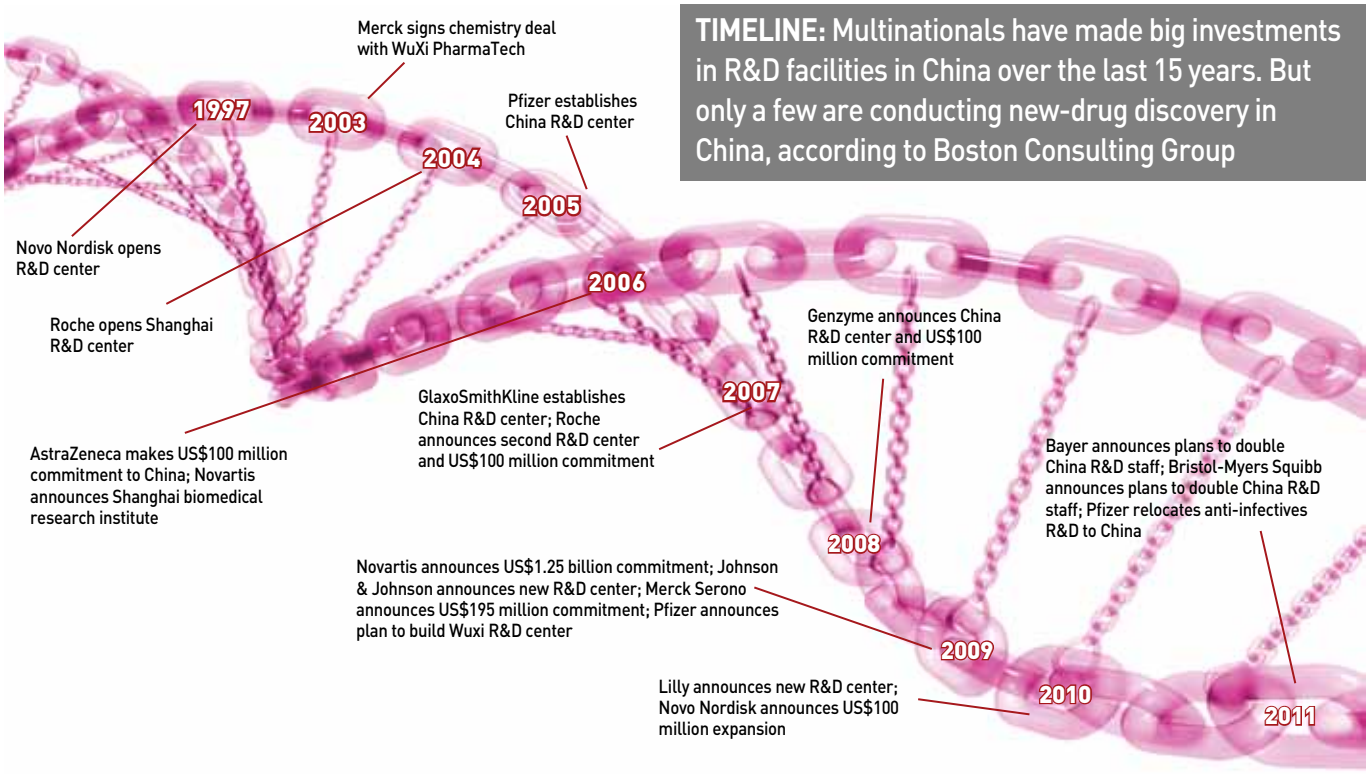
Chinese biotech firms have been closing the gap with these international players in the last few years, thanks to generous support from Beijing. In December, top leaders announced they would invest US$6.3 billion in subsidies for the industry and recruit 300,000 professionals over the next five years. Many overseas-educated scientists have moved back to the mainland, both pushed by the withering effects of the financial crisis on developed countries and pulled by China's booming industry.

For a developing country, China has made remarkable achievements in biotechnology. It was the only developing country to participate in the human genome project; it is building what will be the world's largest genetic databank in Taizhou, Jiangsu province; and it has made a few significant breakthroughs in biological treatments, including introducing the world's first commercialized gene therapy product.

Zhang Weiwei, chief scientist at Sibiono GeneTech, the Shenzhen-based company that makes that therapy, said he believes China is now 10 years ahead of the rest of the world in gene therapies, largely because it lacks the strict regulations that have slowed the industry in countries like the US. Many patients with terminal cancer seek out Sibiono's treatment, which costs about US$20,000 for a two-month course. In contrast, few gene therapy treatments are available in the West: The US halted trials for similar drugs after they resulted in the death of a study participant in 1999 and gave other participants cancer.

Sibiono's case demonstrates that biotech firms do have some structural advantages in China, in that they face less regulation and ethical opposition. Unlike the US and Europe, China lacks any notable ethical resistance to the use of stem cells or even organized opposition to animal testing. And there has been no public conversation to date of risks to individual rights or privacy from the establishment of government-owned genetic databases.

But the number of Chinese firms like Sibiono that make novel biological products remains very small, as the popularity of the biosimilars confer- >>



Source: Boston Consulting Group

» ence in Shanghai attests. For every one of the handful of Chinese companies that have the capacity to innovate, there are hundreds of companies that may never achieve US or EU standards for biological drugs. Instead, they are racing to be among the first to copy an existing drug and win a share of a regional market, perhaps supplying hospitals and pharmacies in one or two provinces.

Following the money

On the whole, most people in the biotech industry say that China's capabilities remain years, perhaps decades, behind those of the US. "In some specific fields, China has an advantage," said Duan Yibing, a policy expert in science and technology at the Chinese Academy of Sciences. "But overall, the difference is still very large."

That's mostly because it takes years to acquire the cutting-edge facilities and technologies that biotechnology requires. Likewise, China is starting to attract back talent, but it still faces a significant shortfall when compared with rich countries. New drugs often take 15 years to progress from research to commercialization, and Chinese companies need professionals that understand every link in that chain. Most industry watchers, like Zero2IPO Vice President Zheng Yufen, estimate

'Those who hypothesize the huge movement of biologics to China are making a very common mistake'
HELEN CHEN, LEK CONSULTING

China's biotechnology is still eight to 10 years behind the West.

And despite bullish statements from Beijing, many enterprises have difficulty obtaining the capital necessary to compete in biotechnology. Since the biotechnology market is still in the early stages, most central government funding goes to research institutes and universities, rather than companies.

Moreover, Chinese venture capital firms are often reluctant to invest in biotechnology because the risk of failure is high and exit opportunities are scarce. Cai, a Chongqing-based biotech researcher, said a venture capital firm had invested US$3-5 million in his former biotech company, but then failed to find an opportunity to exit its investment. "So it became a holding company instead," he said.

The industry has found a promising new model in industry funds, where larger pharmaceutical companies like Eli Lilly and ShangPharma invest directly in promising early-stage technologies. But so far their scale remains limited.

Haves and have-nots

As a result of these pressures, the Chinese market has split in two, with well-funded and more innovative giants on one hand, and smaller, more narrowly-focused players on the other. The market is so diffuse, said Huang of Pharmacons, that these segments don't compete directly. "Yes, the domestic market overall has a share, but they're like a rich cousin and a poor cousin – they actually live separate lives."

The country's large, listed pharmaceutical firms – such as CP Guojian Pharm, Jiangsu Hengrui Medicine, Simcere, 3SBio and United Labs – are still largely focused on biosimilars, but they are likely to gradually shift their focus towards novel products over the next few years.

These companies will also benefit from policies in the 12th Five-Year Plan that aim to build up some of China's larger pharmaceutical firms into national champions. According to an executive at ShangPharma, Simcere alone receives US$6.3-7.9 million from the government

each year. Such companies are also likely to benefit from the 13th Five-Year Plan, which aims to consolidate the industry by eliminating 1,000 less competitive enterprises, said Zhang Fabao, the CEO of biotech industry website Bioon.

The government's primary goal in supporting these top-tier biotech companies is to see them serve the domestic market, mostly by providing cheaper copies of biological drugs that Chinese patients could not otherwise afford. Several are already earning the bulk of their revenue from this strategy: 3SBio has garnered a 44% share of the local market for epoetin alpha, a biosimilar that mimics Amgen's multi-billion dollar drug Epogen, which helps to stimulate red cell production in patients undergoing chemotherapy and kidney dialysis.

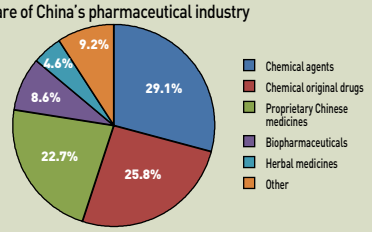
Thus far, China's big pharmaceutical companies have focused on the simpler biological drugs, like proteins. But some are already turning their focus to the more expensive and complicated biological treatments, such as the monoclonal antibodies that are becoming standard treatments for cancer patients in developed countries. One example is Herceptin, a breast cancer drug that is covered by insurance companies in the US but remains out of reach financially for 85% of Chinese breast cancer patients.

Once companies like CP Guojian Pharm, Jiangsu Hengrui Medicine and Simcere gain steam, they could start competing with multinational pharmaceutical firms, most likely starting in other developing markets like Russia, Thailand and India. Chinese companies who master monoclonal antibodies in particular would have a big cost advantage, said Zhang of Bioon. "The technology is still at an early stage, and international products are expensive. So Chinese companies could compete on price," he said.

But their success is still far from assured. While Chinese companies are investing in catching up, foreign com- >>

A small piece of pie

Share of China's pharmaceutical industry



Source: NBS, 2007

GM me: A hungry nation debates the merits of genetically modified food

Though economic development has forced China to give up many old prerogatives, the country has stubbornly clung to a philosophy of agricultural self-sufficiency. Leaders still maintain the old pre-reform-era quota of growing 95% of the country's edible grains (though production has sometimes dipped below that level in recent years). Their steadfast adherence to the quota is even more remarkable given that China has only 7% of the world's arable land, a percentage that will keep shrinking over the next decade due to urbanization and environmental degradation.

The insistence that China can feed itself stems to some extent from a faith in the potential of genetically modified food. China has intensively researched GM foods since the 1980s. In total, the country has approved 37 genetically modified products for sale and import, including strains of canola, tomatoes, cotton, maize and rice.

In the coming decade, GM production is set to accelerate. Beijing plans to pump US$3.14 billion into the sector before 2020.

Feeding the world

The potential benefits of GM crops are significant: They can be coaxed into adopting many positive traits, including higher yields and greater resistance to infection and drought. Clive James of the International Service for the Acquisition of Agri-Biotech Applications estimates that GM rice alone will boost the incomes of 100 million Chinese farmers by US$4 billion a year.

Many people – including officials at the US Food and Drug Administration – argue that genetically modified foods are safe for human consumption. But there are some studies that cast this into doubt.

Research by the World Health Organization indicates that GM foods have the potential to provoke allergic reactions, transfer harmful genes to human body and crossbreed with other plants. According to a 2009 report by the American Academy of Environmental Medicine, several animal studies indicated serious health risks associated with consuming GM foods, including infertility, immune problems and accelerated aging. Even the inventor of China's GM rice strain, Yuan Longping, argued that it will take two generations to confirm that GM foods are entirely safe.

A Greenpeace survey of 1,300 Chinese suggests that concerns about GM foods are prevalent among urban youth: 60% of the respondents, all aged between 18 and 35, opposed GM foods. For the rest of the country, genetic modification is still a murky and somewhat ominous subject. To dispel this fear, China's Ministry of Agriculture has stepped up its efforts to publicize the safety of GM foods, including a booklet published in June called "100 Questions About GM Crops."

Mixed messages

In the meantime, China's agricultural lobby has occasionally used this resistance to GM foods to its advantage. In 2010, COFCO rejected 5.4 tons of GM corn imported from the US because the strain was not among the 11 types authorized in China. Seed company Monsanto has also complained about a lack of consistent policies from the government.

"The ministry [of agriculture] advocates the commercialization of GM foods in China, but at the same time bans it from our tables," activist Yang Fangzhou told the *Global Times*.

Either way, illegal genetically modified rice may already be widespread in China. As early as 2006 and 2007, European officials reported that products made with illegal genetically modified rice were being exported from China to the EU. In 2010, Greenpeace said that it had found GM rice being planted without government intervention in Hubei and Hunan province, as well as tainted samples at processing enterprises that source their rice from China's state reserves.

These examples suggest it will be hard to hold back the tide of genetic modification. With 1.34 billion mouths to feed, Beijing is unlikely to try. ◆

Infant industry: China's ethical debate over genetics differs wildly from the West

In a low rise building in China Medical City, a sprawling industrial park in the eastern Yangtze Delta, scientists are building one of the world's largest stores of genetic information. Biobanks like this one hold the promise of unlocking trends in genetic heredity and creating potent new biological drugs.

The potential benefit of these banks has grown in recent years due to a dramatic drop in the expense of doing genetic research. The cost of sequencing a human genome plunged from US$8.9 million in July 2007 to just US$10,500 three years later. Industry watchers expect the price to fall below US$1,000 within a year or two.

The data surrounding human sequencing is set to explode within the next decade. As genetic information becomes more readily available, conflicts over how to use and store this information are also bound to increase. Many in the West fear that genetic data could be misused to persecute those with certain genetics traits or defects, perhaps resulting in insurance company rejections or selective abortions. And with biological medicine still in its infancy, it is unclear whether doctors should disclose to patients the presence of genetic proclivities for diseases they may never get.

In the vault

At the heart of this debate is how biobanks collect, store and use genetic information, and whether these processes infringe the rights of those who donate their genes.

China's earliest biobank, the Guangzhou Biobank Cohort Study (GBCS), provides a case study in the pitfalls of this process. Wen-Ching Sung, a professor of anthropology at the University of Toronto, described how GBCS collected samples in 2003 through a partnership with a welfare association for the elderly, using methods that would merit a lawsuit in the West.

In one incident reported by "Nanfang City News," GBCS collected genetic data from 42 elderly association members who had come for a free medical exam. Many were illiterate and none understood that the samples would be used for research. "They came with interests because the director of the [welfare association] branch told them that this was a 'deluxe medical exam free of charge,'" wrote Sung.

Such collection methods would undoubtedly raise hackles in the West. In China, however, there were no protests or public outrage over this or similar incidents. This should not be taken as a sign that Chinese people have no regard for privacy, said Sung. Rather, it indicates that the Chinese media has yet to lead the public in any conversation about genetic privacy.

Guarding the gene pool

The conversation that has taken place in China has been surprisingly different. It has centered around the threat of "bio-piracy," or the potential for foreign countries and companies to abscond with Chinese genetic data.

The controversy began in the late 1990s when Xu Xiping, the director of a Harvard University population genetics program, began traveling to remote areas of Anhui province with the goal of collecting 200 million DNA samples. Xu, an Anhui native, intended to analyze the sample for diseases like diabetes, obesity, hypertension and schizophrenia in Harvard's laboratories.

But the study never got very far. Virulent essays began to appear in the Chinese media about foreigners poaching valuable genetic resources. That put into motion a movement which culminated in legislation making it nearly impossible to export genetic material from China. Those rules continue to complicate life for multinationals that do clinical trials in China, said Helen Chen, a partner at LEK Consulting.

Thus far, China's ethical debate has differed wildly from that of the West. But questions are just beginning to take shape both within China and abroad, and new conflicts are sure to come to the forefront. "[The debate] is really around, given that genetic data is valuable, can that be misused and misappropriated," said Chen. "And that debate hasn't really been worked through." ◆

>> panies appear to be investing far more in staying ahead. Michael Choy, a principal at Boston Consulting Group, said that most multinational firms invest 15% of their revenue in R&D. China's top-tier pharmaceuticals typically invest 6-10%, while small Chinese enterprises re-invest only 1-2% of revenues, he said.

Meanwhile, multinational companies are also setting up huge biotech research facilities in China in anticipation of the growing pool of talent, government support and the future increase in domestic market demand. Thus far, eight major multinational firms have announced plans to set up R&D facilities in China, often near Beijing or Shanghai.

However, the cheap labor advantage China has enjoyed in many other sectors gives it less of an edge in pharmaceuticals. Because the manufacturing process for biological drugs is so complicated, labor cost is not the major consideration for biotechnology firms. MNCs are more likely to search the globe for corporate tax breaks and pools of talented employees. They have found this in places like Singapore, Korea and Ireland, which now have booming biotech industries, said Chen of LEK Consulting.

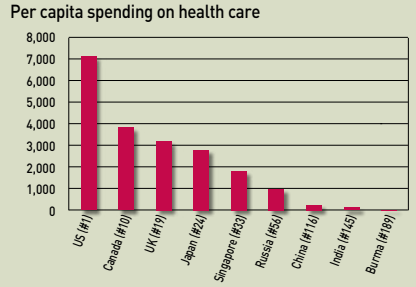
"Those who hypothesize the huge movement of biologics to China are making a very common mistake," said Chen. "They are essentially applying the chemical pharmaceutical analogy to biologics, which has very different economic dynamics. You can't just say that because China cornered Vitamin C manufacturing, then China will do that [in biologics]." As evidenced by generous government grants in the field, China is trying to corner this new market. "But it's by no means assured," said Chen.

Putting the "micro" in innovation

Thus far, it has been easy to deride Chinese companies for a failure to innovate, for simply copying technologies that were

Barefoot doctors

Per capita spending on health care



Source: World Health Organization, 2008

developed through hard work and investment in developed countries. Indeed, many Chinese criticize their country for this. Some even harbor doubts that China can create more than a handful of novel products.

But as long as China's economy continues to grow, these critics are likely to be disproved. There are already a small number of Chinese companies creating novel drugs. The rest are either stymied by a lack of market demand – natural in a country with a per capita GDP roughly equivalent to Jamaica – or systemic barriers that are likely to disappear as the industry develops.

One such barrier is undoubtedly the acceptance of patent infringement. Wang Yanyi, a professor of pharmacy at Guizhou University, illustrated just how widespread this is in the industry: "Most companies don't apply for patents, because it just brings trouble," he said. "If you want to sell your technology, you'll need to apply, but if you want to produce it yourself, it's safer not to. If you apply for a patent, other people will use that patent."

Given China's huge demand for cheaper biological drugs, the domestic industry is likely to continue focusing on reproducing close copies of Western products for the near future. However, the "micro-innovations" that happen during this process should not be discounted. That is especially true in the biotech sector, where small changes in the manufacturing process can result in very different drugs, and a variety of drugs must be developed to treat different people and strains of disease.

The day when China begins trying to enforce intellectual property in the biotechnology sector is probably not that far off – that day will come when its national champions build their own portfolios of novel products. But as the current industry shows, they too may have trouble protecting their original products. When it comes to biology, intellectual property is in essence a murky issue. ◆

COPYCAT: Chinese companies say patent infringement is still widespread

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