Trading on traditional medicines

Developing countries could exploit traditional medicine to kick-start biotech, but only if their products measure up to the demands of Western regulators. Paroma Basu reports.

Traditional medicine marketplace in mainland China

This month, the traditional Chinese medicine Kanglaite Injection is poised to enter phase 2 clinical trials in the United States for the treatment of several cancers, including breast and prostate cancer. The 'drug's' progress will be watched closely by companies planning to transform local medicinal knowledge into biotech medicines. But a handful of traditional medicines developed by biotech companies have crashed and burned in the US regulatory system, raising doubts as to whether such remedies can offer a viable alternative to orthodox drugs in Western markets.

Botanical bellwether

Kanglaite Injection, produced by the Chinese company Zhejiang Kanglaite Pharmaceutical (ZKP; Hangzhou), has come farther than any traditional medicine toward earning drug approval in the West. With $20 million from an undisclosed investor, the company is preparing to enter phase 2 botanical drug trials this month.

Kanglaite is an extract produced from the coix seed (*Semen coicis*), a Chinese food staple. An injectible form of the extract was approved by China's State Drug Administration (SDA; Beijing) in 1996. A best selling anticancer drug in that country, Kanglaite has now been used by over 250,000 Chinese patients for lung, liver, breast and several other cancers. The extract has also been on the Russian market since last year, approved after only a year of clinical trials. According to ZKP, the speed of approval reflected the Russian regulatory authorities' willingness to accept safety and efficacy data from the three-year-long SDA trials in China.

However, according to John Harmer, CEO of ZKP's subsidiary Kanglaite USA (Salt Lake City, UT, USA), the US Food and Drug Administration (FDA; Rockville, MD, USA) is much less open to accepting foreign safety and efficacy data. It took two years and $5 million to get through phase 1, says Harmer, who felt that much of the process was "unnecessary."

Since 1997, at least three other Chinese businesses have embarked on US clinical trials, but the associated cost, time and stringency of the tests have prevented any from clearing phase 2.

The Tasly Group (Tianjin, China) was the first Chinese company to receive FDA approval in 1997 to begin trials for its red ginseng (*Panax ginseng*)-based 'cardiotonic pill' against coronary arteriosclerosis. China's Department of Science and Technology (Beijing) partially funded the trials. But by 2000, the huge cost of international drug trials prompted the government to back out.

Other botanical drugs in the pipeline are faring better with self-generated funds. One remedy on the horizon is a lung cancer medication developed by China's National Corporation of Traditional and Herbal Medicine (CNCTHM; Beijing). The FDA recently approved phase 1 trials for the CNCTHM traditional medicine, an extract of a rare Chinese plant that the organization would not disclose. CNCTHM is collaborating with Botanica Bioscience (Ojai, CA, USA)—which oversees the supply of quality-controlled Chinese herbal products to US companies—for help with ironing out quality control and regulatory issues.

Other non-Western companies attempting to reformulate age-old remedies into modern day drugs (Table 1) include Avestha Gengraine Technologies (Bangalore, India), which is beginning to clinically validate 'ayurvedic cures'—part of the holistic Indian medical system of Ayurveda that dates back at least 3,000

Box 1 East meets West

As regulations change in the West, authorities in developing nations, such as China, are introducing regulations to ensure higher safety standards so that consumers won't be deterred from the traditional medicine market. Under the new regulations, Chinese traditional medicine practitioners and herbal pharmacists must have licenses and manufacturers and herbal farmers have to comply with international manufacturing standards (Good Manufacturing Practice) starting this year. Clinical trials will also be more rigorous, modeled after Western regulatory protocols. China's Ministry of Science and Technology, for instance, has made the modernization of Chinese medicine one of 12 focal points in its current Five-Year Plan. It has also dedicated an entire technology park, in Houzhou, to the modern study of traditional Chinese medicine.

Hong Kong also intends to become an international center for Chinese medicine before the end of the decade. Its government is funding at least 18 Chinese medicine research projects that include clinical trials, development of quality standards and basic pharmacological studies. Hong Kong is building a new laboratory devoted to Chinese medicine and has one of the region's only screening centers to identify promising drug leads from within Chinese medicine. *PB*

years—targeted at obesity and diabetes. All are chasing a global market for natural cures estimated in the billions of dollars (**Box 2**).

Box 2 Supply and demand

With the rising popularity of yoga, acupuncture and the New-Age lifestyle, the Western appetite for traditional, complementary or alternative medicine (depending on what different nations call them) seems insatiable. According to last year's World Health Organization (WHO; Geneva) report on traditional medicine, 70% of Canadians, 48% of Australians and 42% of US citizens have tried traditional medicine at least once[1]. Such remedies also remain widely prevalent in the majority of developing countries; 80% of Kenyans and 65% of rural Indians, for instance, continue to resort to natural cures, according to the WHO report, which estimates the global market to be $60 billion annually. Steve Burrill, CEO of investment firm Burrill & Company (San Francisco) says that investors and biotech companies too are starting to eye the enormous worldwide demand for "wellness" products. It is still too soon to know which player—overseas companies, existing supplement makers, or Western biotechs—will dominate the market, says Burrill. *PB*

Dietary supplements or drugs?

Traditional medicines on the US market have been historically regulated as dietary supplements under the 1994 Dietary Supplement Health and Education Act (DSHEA). Unlike the standard used for prescription drugs, DSHEA puts the onus on the FDA to prove that a supplement poses significant or unreasonable risk of harm rather than on the manufacturer to prove the supplement's safety. The caveat for manufacturers is that unlike pharmaceuticals and recombinant drugs, dietary supplements can only claim to prevent a disease's symptoms, not cure the disease. Elsewhere, the European Union (Brussels) regulates supplements similarly to the US, though the process is faster because a substance's historical use can be used to document safety and efficacy, in the absence of scientific evidence to the contrary.

Manufacturers that opt to designate their products as supplements can bypass expensive and time-intensive clinical trials, thereby getting products to the store shelf more quickly and cheaply. However, the absence of adequate evaluation and safety monitoring systems for supplements has had serious repercussions for the global market for traditional medicine.

In 2000, for instance, the FDA stopped imports of Chinese herbs in the genus *Aristolochia*—used in the manufacture of slimming agents—after reports of kidney failure among users in the United Kingdom, Belgium and Singapore. More recently, the FDA in January banned the sale of products containing ephedra. Derived from the Chinese herb ma huang (*Ephedra sinica*), ephedra is an amphetamine-like 'herbal ecstasy,' used to promote weight loss and enhance athletic performance. Although the principal active ingredient of ephedra, ephedrine, had been banned by the FDA in the 1980s when marketed as a drug in combination with caffeine, dietary supplements containing ephedra and caffeine remained on the shelves. Over a hundred reports of alleged ephedra-related deaths, including the high-profile death of professional athlete Steve Belcher in 2003, were received by the FDA before it banned ephedra.

Because of safety concerns, sales of natural remedies, which had experienced a boom from 1994 to 1998, have sunk since 2000, according to Stephen Morrissey, Botanica Bioscience's CEO. But because they are supposed to work differently from conventional drugs—as 'restoratives' rather than treatments for symptoms—traditional medicines, Morrissey argues, might actually outperform Western pharmaceuticals for treatment areas such as chronic degenerative conditions.

But for natural remedies to graduate from the status of untested supplement to approved drug, regulatory officials have to recognize the specific nature of such remedies, says Morrissey. For now, "the two extremes in the US regulatory environment—no premarket approval and pharmaceutical drug approval—don't really suit the development of the highest quality of botanical drugs."

Alternatives on trial

Despite the expense and Western regulators' unfamiliarity with traditional medicines, a few manufacturers are still submitting their products for clinical evaluation, taking on formidable regulatory challenges. Most pharmaceuticals and recombinant drugs assessed by the FDA are single chemical or biological entities, which facilitates assessing a drug's appropriate dosage and risk/benefit ratio.

Traditional and herbal medicines, however, comprise cocktails of complex natural compounds. In those few instances where the FDA has regulated combinations of conventional pharmaceuticals, the product has been a new drug in tandem with an already approved drug. Herbal medicines therefore represent uncharted regulatory territory.

In 1997, the FDA proposed guidelines on 'botanical drugs,' or pharmaceutical drugs that comprise mixtures of vegetable matter, including plant materials, algae and macroscopic fungi[2]. The botanical approval route is modeled on the existing drug approval route of clinical trials. However, if a product has been legally marketed as a dietary supplement, companies can show its safety using existing scientific literature, rather than going through rigorous preliminary trials.

Table 1 Selected companies developing botanical drugs

Company	Focus areas (drug)	Stage of development
Zhejiang Kanglaite (Hangzhou, Zhejiang)	Cancer (Kanglaite Injection)	Phase 2
CNCTHM (Beijing, China)	Lung cancer	Phase 1
Phytomedics (Dayton, NJ)	Viral diseases, diabetes, obesity, cardiovascular disease, Parkinson's	Preclinical
Phytoceutia (New Haven, CT)	Cancer, neurovascular disease	Preclinical
Harmonex (New York)	Lung cancer (HMX538)	Preclinical
The Tasly Group (Tianjin City, China)	Cardiovascular disease (Danshen Dripping Pill)	New investigational drug status
Avestha Gengraine Technologies (Bangalore, India)	Diabetes, obesity	Preclinical

Source: Company websites

When the guidelines first surfaced, a handful of US entrepreneurs promptly attracted venture backing and began to scour natural systems for promising drug leads. At the forefront of such efforts were such companies as Ancile Pharmaceuticals (San Diego, CA, USA) and Shaman Pharmaceuticals (S. San Francisco, CA, USA). But most such operations eventually folded.

Ancile was in the middle of phase 2 trials for two neurological and one cardio-renal drug before running out of money following September 11. The problem was a weak economy but also the uncertainty investors felt about working with regulatory guidelines that were—and remain—unfinalized. "Botanical drugs are a really new marketplace and we were a pioneer at a time of [regulatory] uncertainty," says Janice Thompson, past CEO of Ancile. Thompson is now senior vice president of Herbalife International (Los Angeles, CA, USA). No botanical drugs have made it to the US marketplace but according to Thompson, between 10 and 20 botanical drugs are undergoing serious clinical development.

Meanwhile, the FDA's Botanical Drug Products Office cannot say when the proposed botanical drug route will be formally adopted, stating in an unsigned written statement to *Nature Biotechnology*, "we are not convinced that the treatments that have been used in alternative medicine should be subject to different requirements than other types of products."

In December 2003, the European Parliament adopted new legislation that makes it easier for traditional medicine makers to show efficacy in the EU member nations[3]. For limited therapeutic indications, and in the absence of adequate clinical data, companies have the option of demonstrating safe use of a 'traditional medicinal herbal product" for 15 years within Europe and for at least 30 years in its community of origin.

Canada also opened the doors of its new Natural Health Products Directorate in January. In the absence of clinical safety data, the directorate will now consider entry of a natural remedy if traditional references—like translated Sanksrit texts or anthropologically validated oral traditions—can prove that it has been safely used for at least 50 years. While Western regulatory agencies are rethinking regulatory practices, developing countries are inching closer to Western-style regulation (**Box 1**).

Hopes and doubts

While the developed world decides how best to allow entry of natural medicines, Chinese traditional drug makers have mixed views on the fate of natural drugs in the West. Faced with the formidable expense and time associated with US clinical trials, natural drug marketers may target Western countries like France, which has looser regulatory regimes than the FDA, says Ji Shen, a senior Chinese researcher at the Shanghai Institute for Drug Control. In France, businesses can sell traditional medicines and label them for indications based on traditional use and historical evidence. But in the end, Ji believes few traditional drug makers really intend to foot the estimated $900 million required for US drug development: they might just go through the preliminary motions to boost a drug's fame within their domestic market.

However, Han Pei, chief of technical marketing at CNCTHM, is more optimistic that traditional drugs can one day emerge in the United States. By communicating extensively with FDA officials about how traditional medicines work, and promoting only simple formulas rather than complex concoctions, she believes Chinese entrepreneurs can crack the US market. "FDA scientists have started to understand us. Now we just need one or two successful examples," says Han.

Kanglaite USA's John Harmer is confident that he can steer Kanglaite Injection to its successful debut as a US-approved botanical drug. But for that to happen, the FDA and the politically powerful pharmaceutical industry—which, he says, have "rigidly resisted" botanical drugs—will have to soften their stance. "The attitude of medical professions and regulatory offices is slowly evolving," he says. "This is motivated by the patients themselves who are demanding that they have the opportunity to use these products." In order for developing countries to exploit and transform traditional knowledge into new businesses, they will also have to confront intellectual property protection issues (**Box 3**).

Several Western pharmaceutical executives are also hopeful that bringing scientific rigor to the study of traditional medicines will brighten the future of natural healing. "There has been this…view that the botanical drug area is low-grade science," says Frank Sciavolino, past head of Pfizer Pharmaceutical's defunct botanical drugs division, and now a senior consultant for Decision Options (Groton, CT, USA). "Now the key thing is to bring new technologies and high-powered science to bear. And I believe that's definitely going to happen."

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Box 3 Protecting local know-how

Organizations and indigenous cultures are increasingly aware of the importance of documenting and classifying inventions based on traditional knowledge. The World Intellectual Property Organization (WIPO, Geneva, Switzerland), has an open-access database on Chinese Medicine on its website, and is working on a second one for Ayurveda, says Francis Gurry, WIPO's deputy director general. However, such public documentation, or 'prior art,' blocks new patents and commercialization efforts. To get around this, countries such as China and India are updating laws and patenting national resources themselves. By doing so countries can retain financial control over future licensing activities. China is farthest along, with over 1200 applications filed, the bulk of which are domestic.

To thwart 'bio-piracy'—misappropriation of a population's knowledge and biological resources by corporations—governments and indigenous peoples have demanded a cut of profits earned by bio-prospecting companies. Without guidance conventions in the eighties and nineties "people went anywhere and took anything," says Gary Eldridge, CEO of Sequoia Sciences (San Diego, CA, USA). Sequoia works with the Missouri Botanical Society (St. Louis, MI, USA), which serves as a middleman between the company and the Gabonese government. Sponsoring educational trips and providing the country with a cut of revenues gives Sequoia free rein to explore Gabon's rich biodiversity, without negotiating directly with the government. "The wave of western companies going into other countries to mine for natural resources is over," Eldridge says. *PB*

1. World Health Organization Secretariat. Traditional Medicine (WHO, Fifty-Sixth World Health Assembly, A56/18, March 31, 2003) (http://www.who.int/gb/EB_WHA/PDF/WHA56/ea5618.pdf).
2. Center for Drug Evaluation and Research, US Food and Drug Administration. Guidance for Industry Botanical Drug Products. *Fed. Register* **65**, 49247–49248, 2000. (http://www.fda.gov/cder/guidance/1221dft.pdf).
3. European Parliament. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (*Official J. Eur. Commun.*, **L311**, 67–128, 2001. (http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_311/l_31120011128en00670128.pdf).