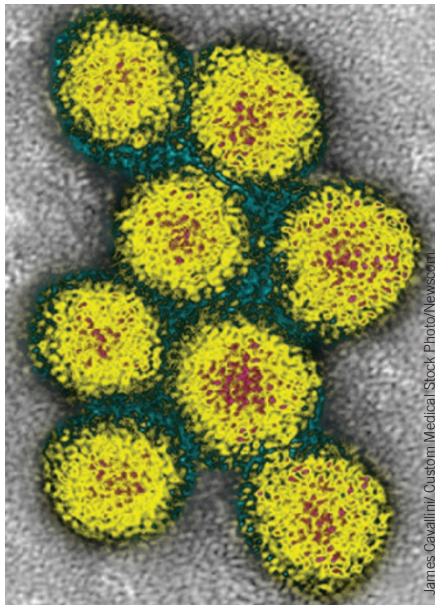
Chinese vaccine developers gain WHO imprimatur

China has passed the World Health Organization (WHO)'s vaccine regulatory assessment, an approval that gives local manufacturers a green light to enter the global vaccine market. On March 1, WHO stated that China's State Food and Drug Administration (SFDA) complies with international standards for vaccine regulation. As a result, vaccines coming from China now have the imprimatur of international recognition, both for exports and domestic sales, says Peicheng Liu, a spokesperson of Beijing Sinovac. But keeping up with international standards may erode China's price competitiveness.

In the process of obtaining WHO approval, the SFDA revised indicators such as the overall vaccine approval framework; marketing authorization and licensing; post-marketing surveillance; lot release; laboratory access, regulatory inspections of manufacturing sites and distribution channels; and authorization and monitoring of clinical trials. "Compliance of the SFDA with international standards is the first step in a process that should see Chinese vaccine producers making a significant contribution to meeting the world's vaccine needs in the near future," says WHO representative in China, Michael O'Leary.

The WHO green light is seen as important because the Chinese vaccine industry has been plagued by scandals. In March 2010, nearly 100 babies in Shanxi province became sick or died after receiving defective vaccines for hepatitis B virus and rabies virus, though the government denied the link. This incident, followed by a problem with substandard rabies vaccines made by the Jiangsu province–based Ealong Biotech, eroded public confidence.



China's first export is likely to be a vaccine against Japanese encephalitis, a mosquito-borne disease caused by a flavivirus (pictured). It is the leading cause of viral encephalitis in Asia.

Validation that the Chinese authorities adhere to WHO standards could go some way to restoring public's confidence. "The approval will enable Chinese vaccine makers to better know international norms and practices, which will definitely help improve the vaccine quality in the domestic market," says Zixin Qiu, general manager of Beijing WanTai, producers of Hecolin, the world's first vaccine against hepatitis E virus (HEV), an *Escherichia coli*–produced, recombinant, 239-aminoacid fragment of the HEV capsid protein ORF2 with alum adjuvant.

China is the 36th nation to obtain WHO status, and trails other developing countries, such as India and Cuba. SFDA has tried unsuccessfully to obtain WHO approval several times in the past, but as Xiaofeng Liang, director of the national vaccination office under the Chinese Centre for Disease Control and Prevention stresses, "The WHO's approval does not mean China did not have a well-regulated vaccine industry." The main reason for China's rejection in the past was a lack of a post-sale surveillance system for vaccine side-effects. Because rare vaccine side-effects sometimes appear only when the vaccine is used in a larger general population, the European Medicines Agency and the US Food and Drug Administration requires post-market surveillance.

"Vaccine makers feared that once they reported some cases the public might refuse to take their vaccines," an employee at one of China's largest vaccine makers, who wished to remain anonymous, told *Nature Biotechnology*. The open reporting of side effects is likely to remain a problem. The system set up for WHO

Table 1 Selected vaccine manufacturers in China

Company name	Vaccines on the market	Vaccines in development
Beijing WanTai Biological Pharmacy Enterprise	No vaccines on the market	Recombinant vaccines against HPV and HEV
Beijing Tiantan Bio	HBV, diptheria toxoid-pertussis, polio, measels, mumps and rubella, Japanese encephalitis and H1N1 flu vaccines	Recombinant HBsAg and EV-71 vaccines
Shanghai Fudan-Yueda Bio-Tech	No vaccines on the market	Therapeutic vaccines (antigen-antibody–DNA immunogenic complexes) against HBV, HCV and TB
Shanghai United Cell Biotechnology	Oral recombinant cholera toxin B subunit/inactivated whole-cell *Vibrio cholerae* (OraVacs; enteric-coated capsule)	
Sinovac Biotech	Healive (inactivated HAV vaccine), Bilive (combined inactivated HAV and HBV vaccine) and Anflu (trivalent inactivated influenza vaccine), H1N1 flu and Japanese encephalitis vaccines	Pneumococcal conjugate and enterovirus (EV)-71 vaccines
Starvax International	No products on the market	SV8000 prophylactic vaccine for SARS coronavirus; proprietary recombinant adenovirus vaccine
Bio-Bridge Science with the Chinese Academy of Medical Sciences (Beijing) and the Institute of Basic Medical Sciences and Beijing Institute of Radiation Medicine (Beijing)	No products on the market	Human papillomavirus polyvalent vaccine and preclinical study for HIV-papillomavirus vaccine
Shenzhen Chipscreen Biosciences with DNAVEC (Ibaraki, Japan)	No products on the market	Codevelopment agreement for DNA therapeutic vaccine for AIDS

Updated from *Nat. Biotechnol.* **26**, 37–53, 2009

CMV, cytomegalovirus; HAV, hepatitis A virus; HEV, hepatitis E virus; HTLV, human T-lymphocyte virus; Ab, antibody; HCV, hepatitis C virus; HDV, hepatitis D virus, HIV, human immunodeficiency virus; HBV, hepatitis B virus; HPV, human papilloma virus; SARS, severe acute respiratory syndrome; TB, tuberculosis.

IN brief

GM bananas

Uganda has launched field trials of its own genetically modified (GM) bananas in an effort to counter a disease that is devastating plantations in the Great Lakes region of Africa. The GM bananas are genetically engineered to resist the *Xanthomonas musacearum* or BXW, a wilt-causing bacterium that destroys the entire plant. Scientists at the National Banana Research Program in Kampala, led by Wilberforce Tushemereirwe, obtained three banana varieties resistant to BXW by transferring two different sweet pepper (*Capsicum annuum*) genes into bananas—one encoding the hypersensitivity response–assisting protein and another the plant ferredoxin like protein. Results from the field tests, carried out at the National Agricultural Research Laboratories Institute in Kawanda, are expected by the end of 2011. "The next step is a multilocation field trial that will take a further two years," says Leena Tripathi, a biotechnologist from the International Institute of Tropical Agriculture in Nairobi, Kenya, also involved in the project. Support comes from the Gatsby Charitable Foundation, African Agricultural Technology Foundation and USAID. The transgene patent holder, Taiwan's Academia Sinica based in Taipei, issued a royalty-free license for commercial production in sub-Saharan Africa. "Crop scientists in the country are making significant progress for both GM banana and drought-tolerant maize. Parliament should now pass the biosafety law needed to permit an eventual release of these improved varieties to farmers," says Robert Paarlberg, a policy analyst at Wellesley College, Massachusetts. *Anna Meldolesi*

IN their words

"Zombie products are never very much fun." Bank Vontobel AG analyst Andrew Weiss comments on Novartis' plans to resurrect a cyclooxygenase 2 inhibitor Prexige (lumiracoxib) banned four years ago. (*Bloomberg*, 5 April 2011)

"There has been a fundamental shift in healthcare industries. Investors no longer place any meaningful value on the pipeline....The stocks are now mostly owned by the likes of people who would own utilities." Bain & Co.'s Tim van Biesen on investors' tendency to shun biopharma's long timelines, as Amgen finally bows to investor demands and agrees to pay dividends for the first time. (*FierceBiotech*, 18 April 2011)

"We were shocked to find out that the FDA is often one of the greatest impediments to job creation." US Rep. Darrell Issa, speaking at a recent public forum, takes aim at regulators for holding back the growth of the biotech and pharma industries. (*The San Diego Union-Tribune*, 22 April 2011)

compliance is a voluntary one, and many domestic vaccine makers are likely to remain reluctant to collect and report side effects of their vaccines. "The Chinese watchdog should increase regulation and education to improve general industry awareness," the insider says.

Liu of Sinovac adds that most Chinese vaccine makers are not familiar with international vaccine purchasers. "It is a long road to sell Chinese vaccines in the global market, despite our lower prices," he says.

Vaccines made in China are indeed cheap. For example, the combined measles, mumps and rubella vaccine is priced by China's National Development and Reform Commission at 20.8 yuan ($3.20) per dose—one-fifth of the price approved by the US Centers for Disease Control and Prevention. Most of these low-cost vaccines are made by the China National Biotec Group, headquartered in Beijing, for the domestic market. But meeting international standards will likely require more expensive materials than those currently employed by manufacturers, says WanTai's Qiu.

To supply vaccines through the United Nations agencies, vaccine makers must now abide by China's new version of good manufacturing practice (GMP), which was released in late February. The new GMP stipulates stricter requirements on sanitation, production process and standardization, in line with requirements adopted by the US, EU and WHO. Most of China's nearly 5,000 pharmas have been asked to pass the new GMP approval in three years and vaccine makers must pass in five years or lose their drug production licenses.

For Western pharma, China's new status presents an interesting prospect. On the one hand, an opportunity exists for technology transfer agreements and partnerships to help Chinese manufacturers maintain compliance with the SFDA. On the other hand, China could gain significant market share in developed nations where vaccine companies, such as Merck of Whitehouse Station, New Jersey, GlaxoSmithKline of London, Pfizer of New York, Novartis of Basel, and Sanofi of Paris currently have a stranglehold, with combined vaccine sales of about $20 billion in 2010.

When contacted by *Nature Biotechnology*, executives at multinational vaccine makers were reluctant to speculate on how WHO approval might influence the business strategy of China's 36 vaccine manufacturing firms going forward. But in the short term, Chinese manufacturers are likely to seek help from foreign firms in improving their operations, particularly as the government begins to open its doors to multinational corporations.

Geneva's International Federation of Pharmaceutical Manufacturers and Associations says the SFDA has "lowered the barriers to entry," allowing foreign investments, buyouts and partnerships in an effort to improve the country's capabilities. To Western pharmaceutical firms, China's domestic vaccine market is an attractive prospect. Novartis, for example, laid down $125 million in March to pick up an 85% stake in Bio-Pharmaceutical, located in Zhejiang, Tianyuan. This vaccine maker produces seasonal inactivated flu vaccines, inactivated bivalent hemorrhagic fever with renal syndrome virus vaccine with alum adjuvant, inactivated Japanese encephalitis virus vaccine and a quadrivalent polysaccharide-based vaccine covering the other four pathogenic meningococcal serogroups, A, C, Y and W-135.

"This is a very positive signal for other foreign companies and investors who wish to follow," says Feng Li, senior vice president of Advanced Pharmaceuticals, a technology transfer consulting firm based in Raleigh, North Carolina, and Shanghai. "There might be an opportunity for them to get their foot in the Chinese market."

GlaxoSmithKline and Merck each believe there is a place for Chinese manufacturers beyond the domestic market in emerging nations, such as Brazil, India, Mexico, Russia and Turkey. Two years ago, GlaxoSmithKline joined with Chinese companies Shenzhen Neptunus and Walvax Biotech to manufacture influenza vaccines and pediatric vaccines, whereas Merck signed a deal in 2010 with Sinopharm Group and its affiliates to work on human papilloma virus and other vaccines. "We believe that great science knows no borders," says Mark Feinberg, vice president of medical affairs and policy at Merck, "and we are impressed with the strong scientific capabilities that are abundant in China."

Chinese manufacturers may help improve access to vaccines in developed nations. WHO prequalification acts as a quality assurance watchdog for low-income countries that lack their own regulatory process. Sabine Haubenreisser, of the European Medicines Agency in London, says, "influenza vaccine supply during the H1N1 pandemic was a bottleneck. China could potentially facilitate supply for global demand in a pandemic."

China's first export is likely to be a vaccine against Japanese encephalitis virus, a virus for which there are currently no WHO-prequalified vaccines, although there are marketed ones made by The Research Foundation for Microbial Diseases of Osaka University (BIKEN) and Vienna-based Intercell, and distributed by Sanofi and Novartis. China expects to have a WHO prequalified vaccine for this disease within one to two years.

Hepeng Jia, *Beijing* &
Karen Carey, *York, Pennsylvania*

Corrected online 8 February 2012.

Erratum: Factors influencing agbiotech adoption and development in sub-Saharan Africa

Obidimma C Ezezika, Abdallah S Daar, Kathryn Barber, Justin Mabeya, Fiona Thomas, Jennifer Deadman, Debbie Wang & Peter A Singer
***Nat. Biotechnol.* 30, 38–40 (2012); published online 9 January 2012**

In the version of this article published in print, the affiliations were omitted. The error was corrected before online publication in the HTML and PDF versions of the article.

Erratum: Amelioration of sepsis by inhibiting sialidase-mediated disruption of the CD24-SiglecG interaction

Guo-Yun Chen, Xi Chen, Samantha King, Karen A Cavassani, Jiansong Cheng, Xincheng Zheng, Hongzhi Cao, Hai Yu, Jingyao Qu, Dexing Fang, Wei Wu, Xue-Feng Bai, Jin-Qing Liu, Shireen A Woodiga, Chong Chen, Lei Sun, Cory M Hogaboam, Steven L Kunkel, Pan Zheng & Yang Liu
***Nat. Biotechnol.* 29, 428–435 (2011); published online 6 May 2011; corrected after print 18 January 2012**

In the version of this article initially published, a line in the abstract read, "repressed by the t interaction…." It should have read, "repressed by the interaction…." The error has been corrected in the HTML and PDF versions of the article.

Corrigendum: Industry continues dabbling with open innovation models

Cormac Sheridan
***Nat. Biotechnol.* 29, 1063–1065 (2011); published online 8 December 2011; corrected after print 8 February 2012**

In the version of this article initially published, Richard Anderson is named incorrectly and so is his affiliation as director of the Initiative for Open Innovation. The source's correct name is Richard Jefferson and he is founder and CEO of Cambia, a not-for-profit biotech research institute based at the Queensland University of Technology, in Brisbane, Australia. The error has been corrected in the HTML and PDF versions of the article.

Corrigendum: FDA panel votes to pull Avastin in breast cancer, again

Mark Ratner
***Nat. Biotechnol.* 29, 676 (2011); published online 5 August 2011; corrected after print 8 February 2012**

In the version of this article initially published, only "ovarian and small cell lung cancer" were said to be among Avastin's current FDA-approved uses. In the US, Avastin is currently approved for advanced colon, non-small cell lung, glioblastoma and kidney cancers. FDA withdrew Avastin's breast cancer approval in November 2011 (*Nat. Biotechnol.* **30,** 6 (2012). The error has been corrected in the HTML and PDF versions of the article.

Corrigendum: Chinese vaccine developers gain WHO imprimatur

Hepeng Jia & Karen Carey
***Nat. Biotechnol.* 29, 471–472 (2011); published online 7 June 2011; corrected after print 8 February 2012**

In the version of this article originally published, in Table 1, Sinovac Biotech was described as having been acquired by Novartis in March. Novartis acquired a different company, Tianyuan, as stated later in the article.

Corrigendum: Intellectual property, technology transfer and manufacture of low-cost HPV vaccines in India

Swathi Padmanabhan, Tahir Amin, Bhaven Sampat, Robert Cook-Deegan & Subhashini Chandrasekharan
***Nat. Biotechnol.* 28, 671–678 (2010); published online 8 July 2010; corrected after print 8 February 2012**

In the version of this article initially published, on p. 671, column 2, the authors state: "Merck has donated three million doses of Gardasil to the Program for Appropriate Technology in Health (PATH) for demonstration trials[14]. Its Gardasil Access Program aims to extend this support to eight LMCs[15]." It should have read: "Merck donated about 130,000 doses to PATH for demonstration studies in India, Peru and Vietnam[14]. Through the Gardasil Access Program, Merck aims to extend its support to LMCs and has pledged to make 3 million doses of vaccine available to eligible countries[15]." In addition, reference 14 should have been Tsu, V. PATH/Seattle, personal communication (2011), rather than Harner-Jay *et al. J. Pharm. Sci.* (2008).