

China's cheap drugs, Africa's high price



ADDED BURDEN: Medicines containing faulty active ingredients can make diseases such as malaria stronger. Here, an 18-month-old malaria patient and her mother in a South Sudan hospital. **REUTERS/MARGARET AGUIRRE/INTERNATIONAL MEDICAL CORPS/HANDOUT**

Unregulated Chinese companies are exporting pharmaceutical ingredients with few or no checks. It puts lives at risk, especially in developing countries

BY MELANIE LEE AND BEN HIRSCHLER

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Philippe Andre, a detective in the murky world of Chinese pharmaceuticals, has some alarming tales to tell.

In May last year, he visited a factory an hour outside Shanghai that supposedly produced a pharmaceutical ingredient. While shown around by men wearing protective clothing and spotless hard hats, Andre noticed oddities: the floor was immaculately clean and some workers sat around idle.



SCRUTINY: The U.S. Food and Drug Administration, which tests and certifies medicines and medical equipment, has identified a number of products which could pose risks from sub-standard active ingredients. **REUTERS/JASON REED**

The factory had an inspection log that spanned eight years with perfect record-keeping, but the handwriting was the same for all those years and not a single page was dog-eared. What's more, while the factory had equipment to dry its product, there were no connecting pipes to funnel steam or waste gases out of the plant.

"Obviously the product was not made there," said Andre, a Belgian who runs a pharmaceutical auditing firm in the eastern Chinese city of Tianjin that advises foreign drug companies buying ingredients in China. The building, he says, was just one of the "showroom" factories intended to disguise China's thriving industry in substandard and counterfeit drugs.

Four years ago, Beijing promised to clean up its act following the deaths of at least 149 Americans who received contaminated Chinese supplies of the blood-thinner heparin.

35%

The share of anti-malarial drugs tested in sub-Saharan Africa that were found to be substandard

Source: The Lancet Infectious Diseases journal, May 2012

But an examination by Reuters has found that unregulated Chinese chemical companies making active pharmaceutical ingredients (API) are still selling their products on the open market with few or no checks.

Interviews with more than a dozen API producers and brokers indicate drug ingredients are entering the global supply chain after being made with no oversight from China's State Food and Drug Administration (SFDA), and with no Good Manufacturing

Practice (GMP) certification, an internationally recognised standard of quality assurance.

"There is falsification of APIs going on, we know it," said Lembit Rago, coordinator for Quality Assurance and Safety in Medicines with the World Health Organisation (WHO). "The regulated markets like Europe and the United States are relatively safe because they have well-resourced regulatory authorities. But the situation is different in places like Africa, where there are a lot of local medicine manufacturers who all use APIs from China."

The export of unregulated drug ingredients may be putting lives at risk, particularly in poor countries where local pharmaceutical controls are minimal. Medicines containing faulty active ingredients or the wrong dose do not work properly and can contribute to the emergence of drug-resistant strains of dangerous diseases, such as malaria.

“We see this as a global crime against public health,” said Edward Sagebiel, a spokesman for Eli Lilly and Co, a multinational pharmaceutical company that says it imposes high standards on its own products, but has seen the unauthorised production of the active ingredients for its drugs by unsupervised Chinese firms. “Because these bulk chemicals are unregulated, they are inherently unsafe.”

China's dominant position in the global market for pharmaceutical ingredients makes the issue both pressing and hard to tackle.

“Illegal ingredients in bulk are a big problem, but nobody talks about it,” said Guy Villax, chief executive of Hovione, an API supplier based in Portugal with factories there and in China, the United States and Ireland.

About 70 to 80 percent of all active drug ingredients – the biologically active component in medicines – originate in China and India, estimate industry experts, with China

“If China for some reason decided to stop exporting APIs, within three months all our pharmacies would be empty.

Guy Villax

CEO, Hovione

accounting for the lion's share. Its export market in these products is worth \$22 billion in annual sales, according to the China Chamber of Commerce for Import and Export of Medicines and Health Products.

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The risks go beyond approved drugs. Unlicensed Chinese chemical firms advertise substances that have been pulled from western markets on safety grounds, such as the weight-loss treatment rimonabant, once sold by French firm Sanofi SA as Acomplia.

Rimonabant was withdrawn in Europe

in 2008 after being linked with users having suicidal thoughts, and it was never approved in the United States. Yet in August, Chinese suppliers were advertising the chemical compound online as available for export. Other unlicensed Chinese manufacturers offer active ingredients still protected by patent in western markets.

Meanwhile China's SFDA – the equivalent of the U.S. Food and Drug Administration – says foreign companies should take responsibility for standards by buying products only from properly certified exporters.

A spokesman for the SFDA told Reuters: “We hope drug watchdogs from importing countries give similar suggestions.”

FLAWED CONTROLS

After the heparin scandal of 2008, Beijing issued a white paper stating that pharmaceutical companies making any APIs, not just those manufacturing APIs for a designated final product, must have a licence from the

CRACKDOWN: Beijing promised to clean up its act four years ago after at least 149 Americans died after using contaminated heparin. In this September 2010 picture, confiscated counterfeit medicines are burnt in Shenyang, Liaoning province.

REUTERS/STRINGER



SFDA. The authorities have also introduced more stringent manufacturing standards.

However, loopholes remain and legal experts say the tougher framework is not strictly enforced.

This year fake versions of Roche's injectable cancer drug Avastin appeared in the United States after transiting Europe. At the time, Roche said it was aware of many cases where counterfeiters had tried to fake other drugs in its portfolio and it was working with law enforcement agencies to stop the trade.

The precise origin of the fake Avastin remains unknown, but in June last year a Shanghai court sentenced 11 people to jail in connection with another case involving bogus Avastin.

A key regulatory weakness in China is the distinction between pharmaceutical and chemical companies. While the former are regulated by the SFDA, the latter, making everything from sweeteners to solvents, are not. Yet many chemical companies also churn out drug ingredients, exploiting a loophole by describing the products as chemicals, which they are, rather than the more specific designation of APIs.

FEMALE VIAGRA

The company New-Sensation Chemical, based in Zhengzhou, the capital of China's Henan province, is one chemical company involved in the unregulated trade. It specialises in producing peptides, a relatively complex class of compounds used in a range of drugs.

Grace Xi, a sales representative, said the company does its own manufacturing, quality control and export. While there is no suggestion its products are substandard, the firm is not GMP-certified or registered with the SFDA.

A New-Sensation product list reviewed by Reuters showed the chemical names of APIs used to treat prostate cancer, bone disease and abnormally low blood pressure, alongside growth hormones used by body-builders to build muscle.

The list also showed bremelanotide, touted as a female version of Viagra, which is still under testing by the U.S. company Palatin Technologies Inc. Though the drug is not yet approved for use in western markets, the product list of New-Sensation Chemical offered the active ingredient for \$13 a vial.

When asked about bremelanotide, Xi said the chemical, though on the product list, was not really for sale. She said the company sold only chemical compounds, "not APIs".

Another chemical company, Jinan Hongfangde Pharmatech (JHP), of Jinan city in Shandong province, had a product list showing at least five patented products for sale. They included tiotropium bromide, a blockbuster lung drug co-promoted by Boehringer-Ingelheim and Pfizer Inc and sold under the name Spiriva, and Eli Lilly's chemotherapy drug pemetrexed, sold under the name Alimta.

A spokeswoman for Boehringer-Ingelheim said the German group was aware there were problems with unlicensed suppliers, adding that it only bought ingredients to make its branded products from trusted sources and was rigorous on quality controls.

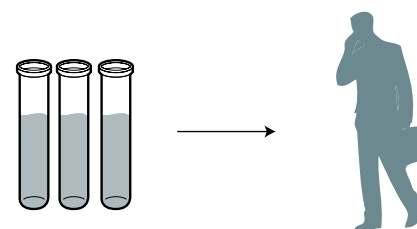
Pfizer and other multinational drug manufacturers, some of which have long-standing deals with respected Chinese companies, also said they were confident in their supplies and only bought from GMP-certified firms.

Allen Li, a sales representative of JHP, said his firm, which has no GMP certification and is not registered with the SFDA, was doing nothing wrong. "We do not infringe on patents, we respect the original manufacturer's research," he said.

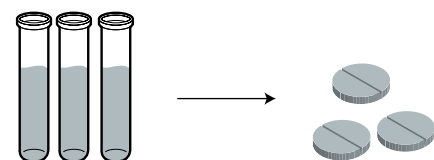
When pressed about the production of APIs still under patent, Li said those substances were not for sale despite being advertised. He declined to answer further questions. "I'm tired of the criticism. Internet, print media, newspapers are keen to criticise," he said.



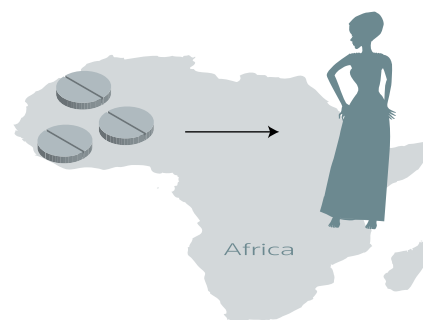
1 An unregulated chemical company in China makes an "active pharmaceutical ingredient" (API), in bulk, without supervision from China's drug watchdog, the SFDA.



2 Unregulated API is exported via an international broker who is sourcing cheap APIs for manufacturers of generic drugs.



3 Manufacturer uses unregulated API to make finished drug, which is supplied to distributors in Africa where local drug controls are weak



4 Drug is given to patients. Ingredients prove substandard. Drug fails to work properly, contributing to development of drug-resistant diseases, including malaria

No senior executive from JHP or New-Sensation Chemical was available for comment.

The rise of the Internet has facilitated exports of drug ingredients. An online search brings up websites offering hundreds of Chinese API sellers. Those not GMP-certified or SFDA-registered are not necessarily substandard, but buyers lack independent quality assurance.

The pervasive presence of brokers in the supply line is another risk. Pharmaceutical companies looking to source APIs in China typically hire middlemen to help them navigate the language, red tape and protocol. That system helps Chinese companies making substandard APIs avoid detection.

Robert Walsh, managing director of biotech advisers Samsara Biopharma Consulting, which has offices in the United States and China, believes big-name multinational drug companies typically select Chinese suppliers on the basis of quality and core manufacturing competence, but says not all buyers are so picky, particularly low-cost generic drugmakers.

"Any number of foreign pharmaceutical companies go no further than looking for API suppliers at CPhI (an international pharmaceutical fair) based only on price," Walsh said.

Reuters spoke to brokers who said an API made by an unregulated chemical company would cost less than one from a company that had a GMP certificate.

"Different (API) grades have different prices. Sometimes we accept an order sheet and we happen to find a factory that can do it cheaper than our factory, we will outsource to them and make a bigger margin," said one broker based in China who sources for a South African outsourcing firm.

In China there are few legal repercussions for broker firms who relabel or misrepresent products, and tracing counterfeit and substandard APIs is extremely difficult.

"There are a lot of brokers who are relabeling (APIs) which means you can't trace where the API comes from and that adds to the risk," said the WHO's quality assur-

ance expert Rago.

Andre, the Belgian drug detective, estimates he has uncovered fraud or misrepresentations in as many as 25 percent of cases where he has been hired to audit factories all over China. "If you can substitute an API that is expensive to make and manufactured at a high level with something that costs much less, then that can happen," Andre said. "It's impossible to give an exact number, but it's not rare. It's a minority, but not tiny minority."

The human cost can be high. Low-quality and fake anti-malarial drugs accounted for more than a third of samples recently analysed in sub-Saharan Africa, according to a study in the *Lancet Infectious Diseases* journal in May. Separate research in the journal *Research and Reports in Tropical Medicine* found Chinese-made drugs to treat malaria and other common tropical infections performed particularly poorly in tests.

"I think Chinese exporters to Africa know that bad products will be less likely

spotted there," said Roger Bate, resident scholar at the American Enterprise Institute, who led the second study.

Sometimes the effects of substandard medicines can be fatal: in 2006 about 100 people died in Panama after taking cough syrups containing a Chinese-made sweetener tainted with diethylene glycol, an industrial chemical used in antifreeze. Other cases, though not immediately lethal, pose long-term health threats. Earlier this year, Chinese authorities announced they had discovered millions of medicine capsules made with industrial gel containing chromium, a carcinogenic heavy metal.

In August, Chinese authorities arrested nearly 2,000 people in a nationwide crackdown on counterfeit drugs, seizing more than \$180 million worth of fake products purporting to treat illnesses ranging from diabetes to high blood pressure and rabies.

Officials are also deploying more technology. By 2015, China hopes to be able to electronically track different types of drugs



SUFFERING: Relatives of people who died after using contaminated heparin, at a hearing in Washington. REUTERS/JIM YOUNG

from their production to end-market to prevent counterfeit and inferior drugs from being distributed, although this will only apply to products traded inside the country.

Despite these advances, legal experts and international officials still think China is not doing enough. Eli Lilly says it is unfortunate that the crackdown does not specifically target bulk pharmaceutical ingredients.

At the U.S. FDA, Commissioner Margaret Hamburg said her agency now had three offices in China and had identified a number of other products, in addition to heparin, where there could be particular "vulnerabilities".

She declined to give details, but brokers

said any API with a potentially lucrative return was at risk if it could be made more cheaply by unregulated companies. Hamburg said: "We do think there's more work to be done in this area and we're very interested in working closely with China."

The United States and Europe both plan to tighten regulations to control API quality better. Washington recently approved the Generic Drug User Fee Amendments, which require inspections of foreign and domestic generic drug manufacturing facilities once every two years.

From next year the European Union will implement a Falsified Medicines Directive, putting the onus on drug companies to prove the purity of the ingredients they use, whether they are produced in Europe or imported.

These new measures will further protect western markets, where the risk of dangerous or counterfeit medicines entering the

legitimate supply chain is already low. But developing countries with weak domestic regulations remain vulnerable.

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POWERHOUSE: China's export market for active drug ingredients is worth \$22 billion in annual sales. Pictured here, Zhengzhou, Henan province, where companies such as New-Sensation Chemical are based. **REUTERS/STRINGER**

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