



SIDE ROAD: A billboard for Abbott in Mumbai. The American pharmaceutical company and hundreds of other firms in India are selling drugs that have been approved by a state but not by the central government. REUTERS/Danish Siddiqui

Broken Health

As combination drugs engulf India, an American pharmaceutical giant profits

By Krista Mahr and Zeba Siddiqui | Filed Dec. 15, 2015, 1:07 p.m. GMT

Part 3: A unit of Abbott Laboratories is marketing a drug in India that doesn't have New Delhi's approval – or that of the U.S. drug authorities. Experts say the misuse of combination

drugs risks boosting antibiotic resistance, turning India into an incubator of “superbugs.”

MUMBAI – Prabhu Dayal arrived at a clinic on the outskirts of Mumbai on a muggy afternoon in July to see the doctor about a cold and cough. The 75-year-old had been feeling unwell for a few days and hoped to get something to treat his symptoms.

He did. But the prescription Dayal left with that day wasn't for any regular cold medicine.

It was for a powerful antibiotic cocktail marketed in India by a unit of U.S. pharmaceutical giant Abbott Laboratories. It is not approved for sale in major markets such as the United States, United Kingdom, Germany, France, Japan and Australia. Medical experts say it doesn't make sense to prescribe the cocktail for cold symptoms. And a government-appointed panel in India recommended to the Health Ministry last year that it not be approved for sale here, citing lack of safety and efficacy data and a high potential for “misuse.”

In fact, the drug has not been approved by the central government, as required by the Drugs Controller General of India (DCGI), the regulator responsible for approving new drugs.

Under India's complex drug-approval regime, many pharmaceutical manufacturers have obtained permission from a single state to make new fixed-dose combination drugs, or FDCs, like the Abbott one - and are selling them in other parts of the country without the approval of the central government. FDCs combine two or more drugs in a single pill.

India's top drug regulator is trying to shut down this avenue. “The first clearance of new drugs which anyone wants to market in India, that has to be given by the national regulatory authority,” G.N. Singh, the Drugs Controller General of India, told Reuters.

But inconsistent enforcement of the drug laws means that hundreds of FDC drugs are being sold in India without the approval of the central government. Policymakers have also now given pharmaceutical companies a chance to retroactively prove the safety and efficacy of these drugs, including the Abbott one. They are currently under review in New Delhi.

Doctors and public health experts both in India and abroad say the proliferation and misuse of antibiotic combinations here may be contributing to antibiotic resistance, making India a potent incubator of so-called superbugs. Some of these superbugs have been found in patients

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who travelled from India to the United States, Britain and other countries.

The drug prescribed to Dayal was Zimnic AZ, which combines two antibiotics in a single pill. Last year, the Illinois-based Abbott's India units had sales of more than \$1 billion. Its revenue in India from combination drugs in 2014 was 24.62 billion rupees (\$367 million), according to IMS Health, a Connecticut-based firm that provides data on the healthcare industry.

In interviews, former and current medical representatives for Abbott said Zimnic AZ has been promoted and administered as a treatment for a wide variety of illnesses, including colds, fevers, urinary tract infections, drug-resistant typhoid and sexually transmitted diseases. Reuters visited chemists who were also selling the drug for respiratory ailments and to prevent post-operative infection. The doctor who prescribed Zimnic AZ for Dayal said the elderly patient seemed to be suffering from a respiratory tract infection.

Combining cefixime and azithromycin - the two antibiotics that make up Zimnic AZ - is risky, said Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics & Policy, a think tank with offices in Washington and New Delhi. By administering these two drugs in a single dose, "you'd be creating strains (of bacteria) resistant to both these antibiotics," said Laxminarayan, who lectures on public health at Princeton University.



OVERKILL: Patients like Prabhu Dayal, a 75-year-old watchman in Mumbai, are being prescribed powerful antibiotic combinations for common cold symptoms. REUTERS/Danish Siddiqui

“Drug resistant strains spread globally,” he said. “They already have. It’s very hard to regulate the movement of people.”

The fact that Abbott and hundreds of other companies in India are able to sell drugs like Zimnic AZ without the central government’s approval is evidence of a health system in disarray. This year, Reuters has documented how the training of doctors in India – the world’s largest exporter of physicians – was riddled with fraud and unprofessional teaching practices. A second article revealed how an Indian doctor facing corruption charges is next in line to head the World Medical Association, the leading international medical ethics body.

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Nearly half the drugs on the market in India last year were combinations. These include medications consisting of three different drugs apiece, doctors said. In the United States, combinations made up 13.9 percent of drugs on the market, while in China the number was 14.4 percent, according to IMS Health. Last year, about 78 percent of combination drugs in India were sold by local firms, with multinationals making up the rest, the health data provider said.

Abbott declined to answer questions from Reuters about why it was selling a drug in India without the approval of the central government.

The manufacture and marketing of Zimnic AZ in India “is aligned with local regulations,” said Varsha Chainani, director of public affairs for Abbott in India. Chainani noted that more than 15 other companies in India are also manufacturing and marketing the same combination under different brand names.

Abbott didn’t respond to questions about whether it was appropriate to prescribe Zimnic AZ for patients like Dayal with cold symptoms. The company wouldn’t say for which specific indications the drug had been approved in India and what marketing instructions have been given to its medical representatives. Abbott declined to say what it was doing to address concerns that combinations like Zimnic AZ may be contributing to antibiotic resistance.

“It would be inappropriate to comment in view of the pending evaluation,” said Chainani, referring to the drug review currently being conducted by the Drugs Controller General of India. “Abbott will abide by the final outcome of the proceedings in this regard.”



UNDER THE MICROSCOPE: Abbott says its combination drug Zimnic AZ is in line with local regulations. But an official in New Delhi says the combination is currently “under the scanner” for safety and efficacy. REUTERS/Adnan Abidi

COMBINATION FEVER

Fixed-dose combination drugs like Zimnic AZ aren’t unique to India. They are used worldwide to improve patients’ compliance in complicated courses of treatment for such conditions as HIV, tuberculosis and malaria. It’s easier to get patients to take one drug than a number of different pills.

Combination drugs are also useful in increasing compliance among the many Indian patients who can’t read, said Sanjay Sikaria, director of drugmaker Suncare Formulations Private Ltd in Uttarakhand state. “FDCs are not bad,” he said. “Rampant misuse of these drugs is bad.”

That’s the problem in India, where there has been an explosion of combination drugs. They have become a way to boost sales and increase market share: More and more companies have tacked on ingredients to existing drugs so they can peddle a new product to doctors and chemists, say people in the country’s highly competitive pharmaceutical sector.

Combination drugs are profitable because of high demand from doctors, who see them as a way to ensure patient compliance, say people in the pharmaceutical industry. Many doctors also see them as providing “quick-fix solutions” that cover multiple possible symptoms with a single pill, said a physician employed by a pharmaceutical company. “The market needs it and demands it,” he said.

Between 2011 and 2014, India’s fixed-dose combination market grew more than 40 percent in rupee terms, according to IMS Health.

A study published in the journal of Public Library of Science (PLOS) in May found that over 70 percent of non-steroidal anti-inflammatory drug (NSAID) combinations, which are used as painkillers, were being marketed in India without central government approval. The authors recommended that unapproved drug combinations be banned immediately.

“We have fixed-dose combinations in every category of drug,” said Anurag Bhargava, professor of medicine at Yenepoya Medical College in the southern state of Karnataka. “The single ingredient versions are harder to find.”

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DELHI TAKES ‘LONGER’

FDCs have grown rapidly in India, in part because over the years pharmaceutical companies have procured licenses from a state to manufacture new drugs, without obtaining central government approval.

The Abbott combination won approval this way, according to Akums Drugs & Pharmaceuticals Ltd, which manufactures Zimnic AZ in Uttarakhand, a state known for its Himalayan peaks and thriving drug manufacturing industry. In 2010, Uttarakhand’s state drug licensing authority granted approval to Akums to manufacture the combination of cefixime and azithromycin, the components of Zimnic AZ, according to the company. Each of those drugs is individually approved by the government. Akums said it also makes the combination for an Indian drug company.

Asked why Akums was manufacturing a drug without the approval of the central government, former company chairman D.C. Jain said state authorities were as qualified as the central government to assess a drug, and that the process of applying for approval from a state and the

central government was similar.

Since getting a state license, Akums said it has filed an application to New Delhi for the combination.

Getting a green light from New Delhi takes “a little longer,” said Jain, who is now a consultant at Akums.

Akums did not respond to a request from Reuters for a copy of the document showing that the combination of cefixime and azithromycin had been approved by the state. When Reuters visited the state drug controller’s office in Uttarakhand, staff could not find a record of the license.

One of several committees convened by the drug controller to review drug cocktails in 2014 recommended that the combination of these two antibiotics should not be approved. The panel found that the drug was “not a standard antibiotic combination” and that “the misuse potential is very high,” according to the committee’s recommendation, a copy of which was obtained by Reuters through a freedom of information request.

After years of intermittent efforts to limit the sale of state-licensed FDC drugs, the government is making another attempt to weed out those it considers “irrational.” More than 3,000 different brands of combination drugs are currently under review in New Delhi, a drug regulatory official said.

Asked about the status of the cefixime-azithromycin combination, G.N. Singh, the drugs controller general, said he could not comment on a specific case. But the drug regulatory official said the combination was “under the scanner” because pairing the two drugs that make up Zimnic AZ “is not appropriate.”

‘IT DOESN’T MAKE SENSE’

Pharmaceutical companies in India employ armies of medical representatives to pitch a drug to doctors.

“We promoted it for typhoid and urinary tract infection mainly,” Jessy Prashanth, a former rep for Abbott in the state of Andhra Pradesh, said of Zimnic AZ. “But we also asked doctors to use it in cases of persistent cough, cold and fever.” Prashanth now works for Alkem Laboratories Ltd, an Indian company that sells the same combination under a different brand name.



ANOTHER CHANCE: India's drugs chief, whose office is located at the food and drug administration building in New Delhi, says he has to give manufacturers a chance to prove that drugs currently being sold without the approval of his office are safe. REUTERS/Anindito Mukherjee

A medical representative working for Abbott in Maharashtra state, who spoke on condition of anonymity, said he only promoted the drug for respiratory tract infections and typhoid. But from visits to chemists and doctors, he was aware it was being prescribed for “everything from soft skin tissue infections, pneumonia, respiratory tract infection, to (urinary tract infection), severe fever, typhoid fever and sexually transmitted diseases,” he said. “It covers most things people go to a general practitioner for.”

The two antibiotics that make up Zimnic AZ attack similar bugs in the body and have the same potential side effects, said Jonathan Zenilman, chief of the infectious diseases division at Johns Hopkins Bayview Medical Center in Baltimore. By coupling cefixime and azithromycin in one dose, he said, patients face a heightened risk of gastrointestinal side effects, like nausea, vomiting and diarrhea.

“It doesn’t make sense,” he said. “The toxicity is duplicative.”

Akums, the manufacturer of Zimnic AZ, said no adverse drug reactions have been reported since the combination has been on the market. For four years after a new medication is approved by the central government in India, drugmakers are required to submit a Periodic Safety Update Report to New Delhi, which should include adverse reactions.

Akums said Abbott regularly submitted update reports for Zimnic AZ. Neither Akums nor Abbott responded to a Reuters request to see the findings.

India’s system for collecting data on problematic drug reactions is weak. The country reported about 37,800 suspected cases of adverse drug reactions to the World Health Organization’s global database last year. China, with a comparable population, submitted close to 214,000 reports for the same period, while the United States reported some 785,000 cases.

DRUG-RESISTANT TYPHOID

Standing in his chemist shop in the Uttarakhand capital of Dehradun, pharmacist Varat Negi said he usually fills Zimnic AZ prescriptions for throat infections and tonsillitis.

“Many doctors prescribe it,” Negi said, pointing reassuringly to the Abbott logo on the back of the blister pack. “It’s a big company.”

Earlier this year, the government reviewed some 6,200 combination drugs, of which some 15 to 20 percent were considered “irrational.”

Government official in New Delhi

Cefixime and azithromycin have been administered together before - but usually as two separate drugs, and to treat very specific problems. The U.S. Centers for Disease Control and Prevention (CDC) says the two drugs may be used together as an alternative treatment for gonorrhea, a sexually transmitted disease.

Results from a study sponsored by the Center of Geographic Medicine and Tropical Disease at the Sheba Medical Center in Israel also suggest a combined therapy of the two drugs was effective in treating drug-resistant typhoid, said Eli Schwartz, the doctor who conducted the research. Israeli doctors started to look into the treatment because travelers were bringing drug-resistant typhoid back to Israel from India and Nepal, he said.

Still, growing drug resistance is a key risk of the widespread misuse of antibiotic fixed-dose combinations, especially in a country like India where prescription drugs are frequently sold over the counter. Bacteria develop resistance to antibiotics when repeatedly exposed to the same drugs over time.

The Central Drugs Standard Control Organization (CDSCO), the regulatory office headed by the drug controller, has tried several times to tame the fixed-dose combination market in the past decade. In 2007, the government ordered states to withdraw 294 combinations that were on the market without the approval of the central government.

It didn't go well. In southern India, drug companies and industry associations took the government to court over the order. The court stayed the withdrawal order, and eight years on, the cases are still pending in the Madras High Court.

Now the drug controller is trying again. In a review of some 6,200 drugs completed earlier this year, only about 40 percent were considered ready for approval by a government-appointed committee. Some 15 to 20 percent were deemed "irrational," according to the drug regulatory official who spoke on condition of anonymity.

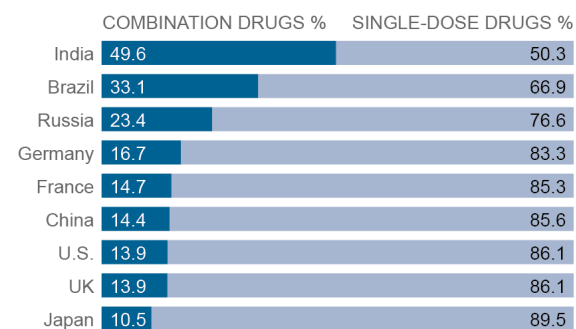
The government has yet to demand that the irrational drugs be removed from the market. Instead, it has issued the equivalent of a show-cause notice to drugmakers, giving them another opportunity to justify these products.

Drugs Controller General Singh told Reuters his office is committed to ensuring patient safety and that he was confident states were no longer granting manufacturing licenses for new drugs. But he said the government was giving drugmakers another chance to make a case for their

A world leader

There has been an explosion of fixed-dose combination drugs in India as pharmaceutical companies try to increase market share.

SALES OF COMBINATION AND SINGLE-DOSE DRUGS IN 2014



Source: IMS Health MIDAS
Note: Figures are for the moving annual total Dec. 2014; totals may not add up to 100% due to rounding.

products.

Akums, the drugmaker that manufactures Zimnic AZ for Abbott, received a government notice in September saying Akums needed to provide regulators with more information, said former company chairman Jain. Otherwise, the combination of cefixime and azithromycin would be considered irrational. Akums provided additional data to the government, and in late November the combination was still under review, Jain said.

Abbott declined to say whether it was informed of the notice sent to Akums.

For Prabhu Dayal, the patient with a cold and cough, Zimnic AZ wasn't a quick fix. Contacted two weeks after he was prescribed the drug, Dayal said he had completed the course but still wasn't feeling well.

So, he went to get another round of Zimnic AZ from the chemist, he said. It was sold to him again – this time without a new prescription.



PANACEA: Former and current medical representatives for Abbott said Zimnic AZ was being promoted and administered for a wide array of conditions. In this 2012 photo, an Abbott rep rides his bike to a doctor's clinic in the Indian city of Pune. REUTERS/Danish Siddiqui

Additional reporting by Steve Stecklow in Mumbai, Ayai Tomisawa in Tokyo, Sujoy Dhar in Kolkata, Sandhya Ravishankar in Chennai, Jatindra Dash in Bhubaneswar, and Aditya Kalra and Rahul Singh in New Delhi.

How India mastered the ‘art of combinations’

By Krista Mahr

Since 1961, India’s drug controller has approved more than 1,200 combination drugs, according to a list published on the website of the Health Ministry’s Central Drugs Standard Control Organization (CDSCO), the national drug regulatory body. But many have also been licensed on the state level without the approval of the central government.

It wasn’t until 1988 that the definition of a “new drug” under Indian law was amended to expressly include the combination of two or more already approved drugs.

Peter Roderick, a lawyer and research fellow at Queen Mary University of London, said “it’s been clear since 1961 that if it’s a new drug, it needs central approval.” Roderick co-authored a Public Library of Science study on fixed-dose combination drugs in India that was published in May this year.

A drug regulatory official said the law has been clear since 2002. That year, an amendment to the statute explicitly stated that to make a new drug, a company required prior written approval of the central government in support of a state license application. Some pharmaceutical makers maintain the requirement wasn’t clear until 2012.

In 2007, the government tried and failed to get close to 300 state-licensed combination drugs withdrawn.

“Indian companies mastered the art of combinations,” said D.G. Shah, secretary general of the Indian Pharmaceutical Alliance, a lobbying group for large pharmaceutical companies. “Certain excesses have taken place.”

In 2012, the government undertook another attempt to exert control over the FDC market. That followed a parliamentary report critical of the functioning of the CDSCO. The report also underlined the health risks posed by unapproved combinations.

“Many FDCs in the market have not been tested for efficacy and safety,” the committee reported.

On the threat of antibiotic resistance, the committee said that unauthorized FDCs “that pose risk to patients and communities...need to be withdrawn immediately due to danger of developing resistance that affects the entire population.”

G.N. Singh, the Drugs Controller General, told Reuters that a government review of combination drugs currently under way would remove any irrational FDCs from the market. “Patient safety is of utmost importance to us,” Singh said.

Broken Health

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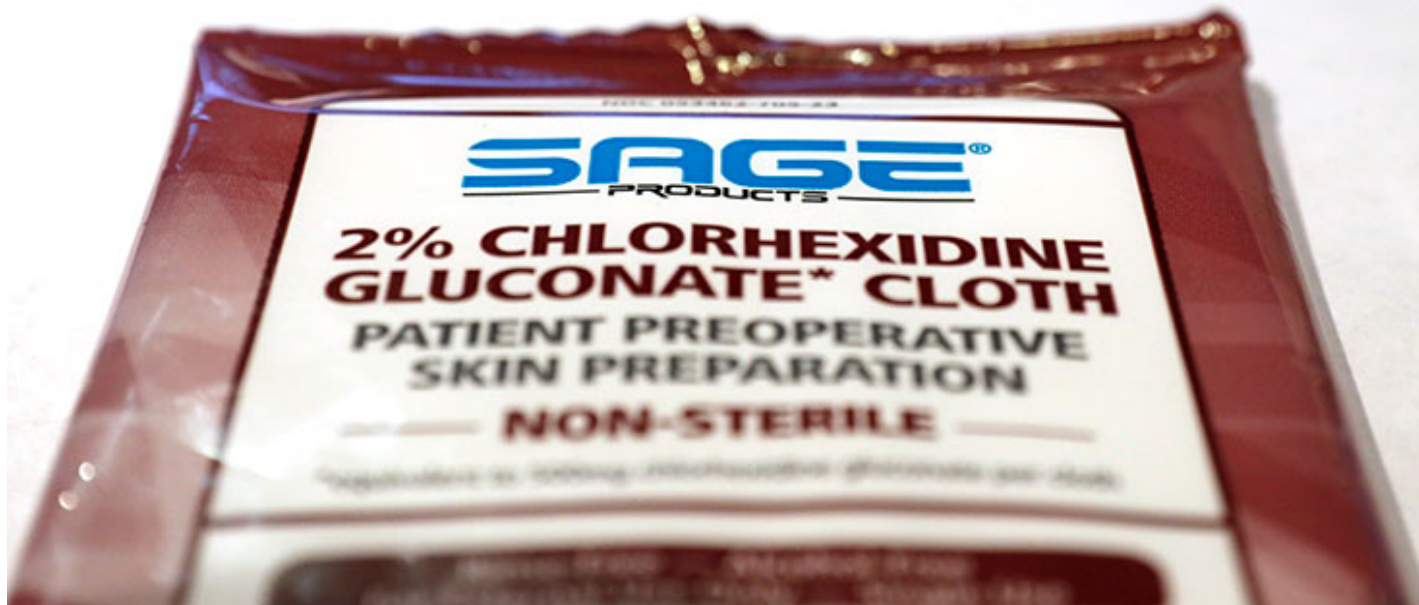


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