90%

of the pharmaceuticals sold in the U.S. are generics

80%

of the active ingredients are produced overseas, where FDA inspections are declining

Huahai factory in Linhai, China

How carcinogens and other impurities end up in the drug supply. By Anna Edney, Susan Berfield, and Evelyn Yu

The chemical N-Nitrosodimethylamine, or NDMA, is a yellow liquid that dissolves in water. It doesn't have an odor or much of a taste. It's known to cause cancer in animals and is classified as a probable carcinogen in humans—it's most toxic to the liver. A single dose of less than a milligram can mutate mice cells and stimulate tumors, and 2 grams can kill a person in days. An Oklahoma man poisoned the family of an ex-girlfriend in 1978 by pouring a small vial of NDMA into a pitcher of lemonade. In 2018 a graduate student in Canada sickened a colleague by injecting the chemical into his apple pie.

NDMA no longer has industrial uses—it was once added to rocket fuel—but it can form during industrial processes at tanneries and foundries as well as at pesticide, dye, and tire makers. It can be found in drinking water disinfected with chloramine. It's in tobacco smoke, which is one reason secondhand smoke is dangerous, and it's what makes eating a lot of cured and grilled meat potentially risky. The U.S. Food and Drug Administration says it's reasonably safe to consume as much as one microgram—one millionth of a gram—of NDMA a day.

In July 2018 the FDA announced that NDMA had been found in the widely used blood-pressure medicine valsartan and started overseeing a recall of drugs from three companies. They'd all bought the active ingredient for their valsartan from Zhejiang Huahai Pharmaceutical Co., one of China's biggest generic companies. The recall has since been expanded 51 times, to include two related drugs, irbesartan and losartan, made by at least 10 companies—some since 2014. Drugs sold to millions of people in 30 countries could be tainted.

Some of the contaminated valsartan contains as much as 17 micrograms of NDMA in a single pill. That's equivalent to eating 48 pounds of bacon. The FDA estimates that for every 8,000 people who took the highest dose of contaminated valsartan for four years, there would be one additional occurrence of cancer. "We had to be honest about that, but it's not a great message for the consumer," says Janet Woodcock, director of the agency's Center for Drug Evaluation and Research. "Throw a couple of lamb chops on the barbecue and you'd find nitrosamine after a good grilling. You have to put this in perspective."

"Valsartan is just the one we caught. Who knows how many more are out there?"

You'd find nitrosamine—a category of carcinogen that includes NDMA—but you wouldn't find 17 micrograms of it. European health regulators put the cancer risk from contaminated blood pressure medicines higher: They estimate that one out of every 3,390 people could become sick.

The FDA has a rigorous approval process for new drugs. Companies conduct clinical trials in humans over several years to prove a drug is safe and effective. But 90% of all medications prescribed to Americans are generics. They're cheaper, they're supposed to work the same way, and they receive less scrutiny right from the start. Companies manufacturing generic drugs have to show only that patients will absorb them at the same rate as the name-brand medications they mimic. At least 80% of the active pharmaceutical ingredients, or APIs, for all drugs are made in Chinese and Indian factories that U.S. pharmaceutical companies never have to identify to patients, using raw materials whose sources the pharmaceutical companies don't know much about. The FDA checks less than 1% of drugs for impurities or potency before letting them into the country. Surveillance inspections of overseas factories have declined since 2016, even as the agency is under pressure to get more generics to market more quickly. In 2008 the FDA opened three posts in China and announced plans to dramatically increase the number of inspectors there. By 2014, it had closed its offices in Shanghai and Guangzhou, leaving only the Beijing office with inspectors who could visit Chinese factories on short notice.

Huahai, the first manufacturer found to have NDMA in its valsartan, is also the one whose product had the highest concentration. When an FDA inspector visited in May 2017, he was alarmed by what he saw: aging, rusty machinery; customer complaints dismissed without reason; testing anomalies that were never looked into. He reported that the company was ignoring signs its products were contaminated. Senior FDA officials didn't reprimand Huahai; they expected the company to resolve the problem on its own. Huahai didn't. The agency didn't try to identify any impurities at that point, and Huahai didn't either. It wasn't until a year later that another company—a customer of Huahai's—found an impurity in Huahai's valsartan and identified it as NDMA. That was when the FDA demanded drugmakers begin looking for NDMA in their valsartan. They found it again and again.

Quality-control problems in the generic drug industry go beyond the visible lapses. The valsartan recall has revealed the once-invisible failures in the chemistry itself, sometimes undetected for months, maybe years. "Valsartan is just the one we caught," says David Gortler, a former FDA medical officer and now a consultant focusing on drug safety. "Who knows how many more are out there?"

Where the FDA's drug approval process is founded on testing and more testing, the regulatory system for generics is built on trust, specifically trust in manufacturers. Woodcock takes exception to that characterization—"In God we trust, everyone else has to bring us data," she says—but it's an accurate description of the complex global system that's developed in the past decade. It's designed to, above all, make and distribute drugs in a cost-efficient manner. It usually functions beyond view. Until there's trouble.

Brackman

PREVIOUS SPREAD: PILL BOTTLE: HELEN SESSIONS/ALAMY. FACTORY: OLIVIER MORIN/BLOOMBERG. THIS SPREAD: PILL: SCIENCE SOURCE. BRACKMAN: PHOTOGRAPH BY WILL WARASILA FOR BLOOMBERG BUSINESSWEEK

Karen Brackman's favorite color is purple. On her good days, she wears an amethyst ring, a purple fitness tracker, and purple-tinted sunglasses. Her toy poodle, which she brought home four years ago, is named Savannah. Her husband, whom she married 30 years ago, is named Tom. Her kids are grown. Her career as an executive assistant at a Nashville company ended happily 11 years ago, when she was 64. Her townhouse sits on Lot 26 of the Rockbridge Cove subdivision in the city of Murfreesboro, Tenn. Her painting studio is on the ground floor; Tom's music studio is on the second.

Brackman's tumor is 5.5 centimeters in diameter. It looks like a black tennis ball and has taken over the left lobe of her liver. The doctor who found it in the spring of 2018 told her it's very aggressive and rare. Then he said he was flabbergasted. She didn't have a history of cancer. She didn't have any risk factors for cancer. She'd had a mild stroke but was otherwise in pretty good health.

A possible clue to Brackman's disease arrived in a one-page letter from Walgreens in July 2018. Valsartan, which she'd been taking daily for at least two years, was being voluntarily recalled by its manufacturer, which had detected "a trace amount of an unexpected impurity," Walgreens said. "This impurity has been classified as a probable human carcinogen."

The letter provided the name of the company behind the recall—Solco Healthcare U.S. Brackman had never heard of Solco. She did remember that a few years earlier, the shape of her blood pressure pills changed. Walgreens said her insurer required the pharmacy to change suppliers. She didn't think any more about it at the time, but now it's one of the things that makes her mad: She didn't have a say.

Brackman found out that Solco is based in Cranbury, N.J., and owned by Huahai. The yellow oval pill she took every night was made in a factory in Linhai, in Zhejiang province, about three hours south of Shanghai by high-speed train.

Linhai, which sits between Kuocang Mountain and the East China Sea, is a prosperous city known for having its own Great Wall and the country's best mandarin oranges. It's been an important center of trade since Japanese ships arrived during the Southern Song Dynasty a thousand years ago. More recently, Linhai's economy has relied on the manufacturing of automobiles, eyeglasses, Christmas lights, chemicals, and pharmaceuticals.

Chen Baohua, educated at Zhejiang University of Technology and a member of China's National People's Congress, founded Huahai in 1989, when he was 26. He started with $5,000 and 12 employees who mixed chemicals in a one-room warehouse. China was becoming an important source of raw materials to the drug industry, offering prices at least 10% lower than its main rival, India. One of Huahai's specialties was ingredients for hypertension drugs.

Chen listed Huahai on the Shanghai stock exchange in 2003, expanded operations to the U.S. in 2004, and in 2006 briefly joined Forbes's list of the 400 richest Chinese, at No. 363, with an estimated net worth of $101 million. The company's sales then were $73 million, and its value on the stock market ▶

◀ $390 million. In 2007, Huahai became the first Chinese company to win FDA approval to export finished pills to the U.S. The drug was a generic treatment for HIV. A banner commemorating the accomplishment hangs outside Huahai's headquarters.

Hypertension affects billions of people, which is why the Swiss pharmaceutical company Novartis AG spent more than $1 billion to develop Diovan, whose active ingredient is valsartan. Diovan went on the market in 1996 and became the best-selling blood-pressure medication in the world. In 2007, it accounted for 20% of Novartis's $24 billion in pharmaceutical sales. It would continue to be a multibillion-dollar drug until Novartis's European patent expired in 2011 and its U.S. patent expired in 2012. Companies were eager to compete with generic versions.

Huahai was among those preparing to supply valsartan to generic drug companies. It would be an important product for Huahai at a crucial time. The company was growing, but not as quickly as some shareholders wanted. It looked like valsartan could help change its fortunes.

The valsartan molecule is simple. A drug prescribed in relatively large doses and taken frequently needs a fairly uncomplicated synthesis to make it cost-effective—in this case, a chain of six chemical reactions starting from basic materials.

The FDA's relationship with manufacturers like Huahai, on the other hand, isn't simple at all. If Huahai wants to make its own version of a generic drug and export it to the U.S., it needs FDA approval. But if Huahai supplies the main ingredient to a company that finishes the drug and sells it in the U.S., it's required only to keep the FDA informed of any changes to the manufacturing process.

In November 2011, Huahai did make a change, a critical one: It switched to a different solvent than the one Novartis had used. There's no making drugs without a solvent; it dissolves the chemicals the drugmaker is combining and then, ideally, is washed out. Huahai's solvent of choice was dimethylformamide, or DMF. In its Chinese patent application, the company said DMF would make manufacturing more efficient, make it easy to control impurities, and assure good quality.

One of those reasons was more important than the others. "The purpose of the change was to save money," Jun Du, vice chairman of Huahai, told an FDA inspector after the recall began last year. "Mr. Du further stated the cost reduction was so significant it is what made it possible for the firm to dominate the world market share," Cheryl Clausen, the inspector, wrote in a 58-page report reviewed by Bloomberg.

The patent application was public, which meant any generic company outside China could copy the steps in Huahai's valsartan synthesis. It appears a handful did, and that this is one reason so much of the world's valsartan supply is contaminated.

The FDA didn't know it at the time, but Huahai didn't follow protocol for the switch. The company first called it a critical change, then just a minor one. It proved to be the former. When DMF dissolved the chemicals at the end of the synthesis, it created a side reaction, which produced a residue that couldn't be cleared out of the drug. The chemists at Huahai either didn't realize that or didn't consider it a potential hazard. A Chinese company hired by Huahai to conduct a pilot test recommended it continue to improve the way it purified solvents before it began commercial manufacturing, Clausen reported. Huahai didn't.

The main responsibility falls on Huahai and every other company to conduct their own safety reviews and to detect and control any impurities. "We have to rely on manufacturers to follow the rules," Woodcock says. "We can't beat quality in. We can't test quality in. People have to be dedicated to making a quality product."

Huahai said in a December statement that it is "taking every step to ensure [its] products remain safe, therapeutically effective, and meet the highest standards." In January the company told investors impurities in its valsartan didn't pose severe health risks. Du says, "My company, which voluntarily initiated the recall, has cooperated fully with the FDA and has provided the agency with considerable information of value in its investigation." The company didn't respond to specific questions about its manufacturing processes. ▶

A Different Way

During an FDA lab inspection just before the online pharmacy Valisure LLC opened for business a year ago, co-founder David Light learned the company was the first—and still appears to be the only—analytical pharmacy in the U.S. That is, the only one that tests the drugs it sells. This was just weeks after the first recall of the blood-pressure medication valsartan.

"Valsartan has added a light to this issue, but these issues have been around for a long time and will become more visible because more people are looking," Light says. "Until something more is done about the system, it's only going to get worse."

The creation of Valisure stems from a personal place. Several years ago, Light's college friend, Adam Clark-Joseph, an assistant finance professor at the University of Illinois at Urbana-Champaign, found that his antiseizure medication sometimes didn't work. His doctor told him the active-ingredient levels in drugs and the rate at which they dissolve in the body vary sometimes, and there was nothing that could be done. Clark-Joseph wasn't satisfied. He called Light, who was working as the director of product management at Thermo Fisher Scientific Inc.'s DNA sequencing division. They cooked up the Valisure model, and three years later launched the company together. It now sells 2,000 pharmaceuticals, which it tests using laser-based technology. If a batch doesn't pass, as about 10% haven't so far, Valisure sends it back.

Carcinogens in drugs are rare; problems with active ingredients aren't. Light says one rejection that particularly sticks out was for levothyroxine, which is used to treat an underactive thyroid and certain types of thyroid cancers. Valisure found doses were too high, and unpredictably so—they varied from pill to pill. The company went through a number of manufacturers before finding one that consistently delivered levothyroxine with correct doses.

Valisure also sees instances of pills that don't dissolve properly, which affects how the active ingredients are absorbed. The pharmacy found multiple batches of lamotrigine—the antiseizure drug Clark-Joseph takes—in which the pills didn't dissolve for 24 hours, maybe longer. "At some point, you have to stop the test," Light says.

◀ Massoud Motamed arrived at Huahai in May 2017 to conduct an inspection for the FDA. The company knew he was coming, which is common for inspections outside the U.S. Du cleared his calendar for the five-day review and stayed close to Motamed the entire time.

Motamed found black metallic and yellow rust particles in some of the machinery. In his report, he wrote that gaskets were discolored, warped, fraying, and missing pieces. Through a translator, Du told him the equipment was old and needed to be replaced.

Motamed identified worse problems. During regular quality testing, the company had found impurities in its drugs, which appeared as spikes or peaks in graphs that resemble the readout of an echocardiogram. Huahai didn't try to identify them. Instead, it omitted those tests from its official reports, retested the drugs, and recorded passing grades.

Du called those spikes "ghost peaks" and said they appeared from time to time for undetermined reasons. Motamed was incredulous. "I indicated that I am not familiar with this concept," he wrote. He concluded in his report that Huahai's decision not to investigate or identify the impurities "casts a cloud of uncertainty over the accuracy of test results used in approval and release of the firm's finished API products." He recommended the FDA send a warning letter, the strongest of the agency's rebukes. That likely would have meant the factory couldn't manufacture any new drugs until it passed another inspection.

The FDA didn't send the letter. Instead, it gave Huahai a chance to resolve the issues without any repercussions. In a memo, obtained via a public-records request, FDA managers explained their decision. The company had passed inspections in 2010 and 2014 and said the test results Motamed questioned hadn't affected the final products. As is always the case with inspectors, Motamed had no say in how the agency evaluated Huahai's response. He didn't even see it; inspectors submit their reports and move on.

Michael de la Torre runs FDAzilla, a research company with a database of agency inspections going back two decades. He says the FDA was too trusting of Huahai given the actions Motamed documented. "This was willful adulteration of testing data," he says. "They were gaming the system." He calculated how often in the past five years the FDA has issued a warning letter when a company's problems include faked results: 25% of the time.

Motamed joined the agency toward the end of the Obama administration, as overseas inspections were peaking. In 2016, the FDA conducted 163 surveillance inspections in China, a record; his audit of Huahai in 2017 was one of 140 in the country that year. In 2018 the number fell to 125, according to agency documents. Motamed left the agency four months after his visit to Huahai. He says it wasn't because he was frustrated, but he is now. "I honestly don't think the FDA realizes the true nature of how the industry operates," he says. "In most cases, business pressures are superseding quality decisions in manufacturing."

Other inspections of factories connected to the blood-pressure pill recall have discovered disturbing evidence of dangerous practices. At a Strides Pharma Science Ltd. facility in Puducherry, India, someone had stuffed discarded quality-control records into a 55-gallon drum in the scrap yard. Other records sat near a shredder. Strides is approved to make losartan, which was recalled in May. The company didn't respond to requests for comment for this story.

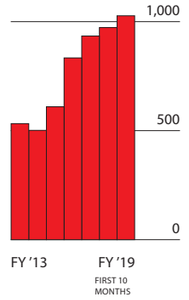
In June the FDA sent a warning letter to another Indian company, Aurobindo Pharma Ltd., saying the company ignored impurities in an active ingredient it produced. The name of the ingredient was concealed by the FDA when it released the letter publicly. Aurobindo recalled contaminated valsartan in January and again in March. The company didn't respond to requests for comment.

An FDA inspector reported that technicians at the flagship facility of Mylan NV in India disregarded about 75% of failing quality checks, for no good scientific reason, over six months in 2016. The inspector suggested that staff were retesting failing drugs until they passed. Because the FDA routinely keeps crucial information in these audits secret, it's unclear which drugs were involved. Mylan recalled its valsartan last November. The company makes its own active ingredient for the drug in India and also sold it to such companies as Teva Pharmaceutical Industries Ltd. Teva recalled its valsartan. Mylan says the warning letter was unrelated to the recall. The facility has since been reinspected and the FDA didn't find any major issues. Teva declined to comment for this story.

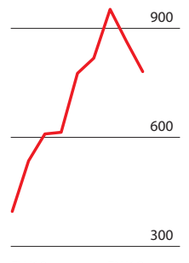
Karen and Tom Brackman watched with agitation as the recalls kept coming. Tom retired from his job as a facilities manager for Dell so he could take care of Karen. By the end of the summer, they began looking for a lawyer. "I knew I wasn't the only one," Karen says. "I want knowledge." The more they've learned, the more frustrated they've become. "The whole system is broken," Tom says. "The FDA hasn't been trying to make sure what's coming from these different countries is of high quality. It's scary." What they've come to realize—what some doctors have come to realize, too—is that the government has a limited ability to regulate the generics industry overseas. It's really supposed to regulate itself. And it's not.

In early 2018, Novartis placed an order with Huahai for 45 metric tons of valsartan to use in its own generic version of Diovan. It wasn't unusual: Novartis had been buying ▶

Generic drug approvals by the Food and Drug Administration



FDA surveillance inspections of drugmakers overseas



FDA FISCAL YEAR ENDED SEPT. 30. DATA: FDA

An FDA inspector recommended issuing a warning letter to Huahai's Linhai factory

◀ valsartan from Huahai since 2012. Clausen, the FDA inspector who visited Huahai last summer, detailed in her report what happened next. After the shipments arrived in Stein, Switzerland, Novartis's scientists conducted tests for residual solvents. What they found worried them: a spike in the data that signaled an impurity. Novartis told executives at Huahai about the spike in June. Clausen wrote in her report that Huahai knew about the data peak and considered it "noise."

Novartis sent samples to another company for more extensive testing. It then informed Huahai that the impurity the company had ignored, and that no other customer seemed to have noticed, was NDMA. Novartis says it notified health regulators of the contamination and recalled its generic valsartan in Europe and Canada.

A probable carcinogen in a medication taken by millions of people manufactured in a factory the FDA knew had problems was a crisis for the agency. Staff scrambled to verify their own test to detect NDMA. The agency says industrial chemists and regulators around the world were surprised to find the toxin in valsartan. They knew there was a risk NDMA could form but didn't think it could survive.

Huahai finally developed a test to detect the toxin—something it should have done when it made the manufacturing change. "They certainly should have caught it, and they should have modified the procedure to correct it," says Kevin Schug, an analytical chemistry professor at the University of Texas at Arlington who's done extensive research on the testing of pharmaceuticals. The company left no records of trying to do either. "Any well-trained analytical chemist would know to check," says Gortler, the former FDA medical officer. "If it's not intentional, it's incompetence. At some point, those are the same."

Gortler says if regulators can't trust manufacturers to catch such impurities, the FDA should inspect the drugs before they enter the U.S. That the agency tests so few is another problem. "It is totally unacceptable," he says. "It is titanically unacceptable."

It seems that none of Huahai's customers anywhere looked for impurities in valsartan until Novartis did—or if they did, they didn't identify what they found. "We in the industry are responsible for testing," says Rick Sachleben, an organic chemist and pharmaceutical consultant. "If we're buying stuff, we have to make sure they're making it right."

To gauge what testing might turn up, consider Valisure LLC, an online pharmacy in New Haven, Conn., that opened in 2018 and tests every drug it orders. It's rejected more than 10% of the medication batches it's purchased, according to CEO David Light. Grounds for rejection could be a drug not having the proper amount of active ingredient, or not dissolving as it's supposed to, or containing impurities. Valisure does sell two versions of valsartan, from Alembic Pharmaceuticals Ltd. in India and Jubilant Cadista in Maryland.

Light says he's spoken with people in the industry about his findings. "The overwhelming response is, 'We know there's a problem, but it's not our problem,'" he says.

QILAI SHEN/BLOOMBERG

"There's no liability at any one point. The whole system is so complicated you could point at anybody. The only element who cares in this whole global supply chain is patients."

In September 2018, the FDA placed the Linhai facility on what it calls "import alert," which prohibits Huahai from selling anything made there to any company that markets Huahai products in the U.S. Canada did the same. European regulators banned Huahai from sending any more valsartan to companies there.

The FDA finally sent a warning letter to Huahai in November. It criticized the company for not trying to identify the impurity earlier and for not anticipating that using DMF as a solvent could cause the problem in the first place. "You did not consider the potential for mutagenic or other toxic impurities to form," the letter read. "You are responsible for developing and using suitable methods to detect impurities. . . . You are responsible for the quality of the drugs you produce."

Clausen raised one other concern about Huahai: In September 2016, a customer had complained about a drug contaminated with a probable human carcinogen. Huahai had reprocessed the rejected batches and sold them to other customers outside the U.S. The FDA didn't identify the drug in the version of the warning letter it made public. Solco issued a press release saying that the drug wasn't valsartan. It was levetiracetam, an epilepsy treatment, and, the company said, the batches that were cleaned up and resold met manufacturing specifications.

"The only element who cares in this whole global supply chain is patients"

The problems at Linhai were so serious and the response so inadequate that the FDA said it had grave concerns about the possibility of cancer-causing toxins in everything manufactured at the facility.

Valsartan was Huahai's second-biggest product before the recall and accounted for 15% of its revenue. In April, Huahai said sales of valsartan had fallen 17%. The company spent 413 million yuan ($58 million) in 2018 to handle the recall and set aside an additional 302 million yuan to compensate its customers. And it reported it was no longer planning on listing another U.S. subsidiary, Prinston Pharmaceutical Inc., on a U.S. stock exchange.

The Chinese government seems to be standing by Huahai, though. From August to October of 2018, the Linhai city government gave 300 million yuan to Huahai in "industrial development assistance funds," the company said. In December, Huahai won six bids as part of a government program to provide lower-cost generic drugs in 11 cities. Huahai said in January that it wants to raise as much as 1.8 billion yuan through a private placement to replenish its working capital and fund a research and development center, as well as a "smart manufacturing" project. By April, Huahai's recall in China was complete.

Karen Brackman doesn't make plans in the weeks after chemotherapy. "When I'm really in pain, it's like I'm on a trolley car and everybody else is on a jet," she says. She had to cancel her painting classes in the Hobby Lobby store nearby. She missed her son's wedding in Australia. She brushes her teeth constantly. "Chemo smells," she says. "It's like a decaying chemical emanating from your cells."

Brackman sued Huahai in April. Her case is part of a bigger, multidistrict suit that will be heard in U.S. District Court in New Jersey. About 140 lawsuits have been filed against Huahai and other drugmakers involved in the recall, as well as pharmacies that filled the prescriptions. There's no trial date yet. Brackman's lawyer, Daniel Nigh of Levin Papantonio in Pensacola, Fla., is also evaluating the claims of more than 500 other people with cancer—liver, stomach, small intestinal, colon, esophageal, kidney—who took valsartan from 2015 to 2018. Huahai says it can't reliably estimate the impact of litigation.

The recalls keep coming. On June 26, No. 52 was issued, and the FDA can't promise that's the last. The agency isn't, however, asking companies or pharmacies to notify patients about possible contamination of batches that expired—or were ingested—before the recall. Woodcock says it's not necessary to worry: "It's not like if you took valsartan you have to be checked for cancer."

The American Medical Association will assess over the next year whether the country's drug supply should be better protected. Independent testing is one possibility. Maybe one day. Improving the quality of imported drugs should be a higher priority, says Peter Pitts, a former associate commissioner at the FDA. "Because if we wait, shame on us."

Congress, for so long focused on the cost of medicine, is starting to look at how to make it safer. It's asked the U.S. Government Accountability Office to conduct a review of the FDA's supervision of factories overseas. The agency is focusing on whether the common practice of recycling solvents may spread any contamination.

"I'm concerned it's like peeling an onion," Robert Kugler, the senior U.S. district judge hearing the multidistrict lawsuit, said in a June conference with the lawyers. "The more regulatory agencies look into more generic brands, the more we're going to find. There's no good way around it. It's a mess."

Until recently, regulators were confident they were properly assessing the potential risk in generics production. Now they're realizing that a system so dependent on trust and self-regulation has vulnerabilities. They know the process sometimes ends with potentially dangerous pills in bottles. Now they have to uncover how it begins. <BW> With Dong Lyu