HEALTH

Bad bargain

All of us want cheaper medicine—but not if it costs us our health. Troubling reactions and a series of recalls are making some doctors wonder, Are generic drugs as safe as the FDA says they are? SELF investigates.

By AUTHOR
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Just when Beth Hubbard should have been feeling great, her health fell apart.

A 34-year-old housewares designer in the St. Louis area, Hubbard had recently gotten married. She liked the creativity of her career. And she'd conquered her mild depression and fatigue with a combination of exercise, rest and medicine, including the antidepressant Wellbutrin XL. But in the fall of 2006, shortly after she refilled her prescription—her pharmacy giving her this time Budeprion XL, a generic version of the drug—her good health gave way.

Within a month, she had gained 15 pounds, couldn't sleep well, developed gastrointestinal problems and felt such extreme fatigue and lack of motivation that she thought about quitting her job. She cried and called in sick for days at a time. "I chalked it up to exhaustion after the whirlwind of the wedding and honeymoon," Hubbard says.

Yet she wasn't getting better. Her doctor referred her to four specialists, but none, she complains, "were really listening to me—they were just anxious to give me another drug." They diagnosed her alternately with severe allergies, a heart murmur, a slow thyroid, irritable bowel syndrome, gluten intolerance, mononucleosis and chronic pain. She cycled on and off different drugs: Ambien to help her sleep at night; Provigil to keep her awake during the day; Allegra, Zyrtec and Nasacort for allergies; Lexapro, Zoloft and Xanax for anxiety and depression; Zelnorm for bowel problems. And she continued on the Budeprion XL the entire time. "I was fighting for almost a year with the insurance company over all the tests and therapy I needed," Hubbard adds.

After eight months of struggling with her mystery ailments, she was out to dinner with a friend and mentioned that she needed to refill her prescription. Her friend said she'd recently gone off Wellbutrin and had some leftover pills Hubbard could use.

Within a week, Hubbard's troubling symptoms vanished. Her energy came roaring back. And that is when she finally connected the dots: Her problems had begun mere days after she first took the generic. Because generics had always worked well for other conditions, she says, "I never even gave it a second thought or mentioned the pharmacy's switch to my doctor." Until now.

She called her doctor to complain about the generic and request a new prescription for the brand name only. The nurse's response floored her. "Yes," the nurse said matter-of-factly. "We hear that all the time."

Why your M.D. is worried

If you took a prescription pill recently, odds are it was generic: Nowadays, generics constitute almost 70 percent of all the prescriptions dispensed nationwide, racking

up $58 billion in sales in 2007. Anxious to cut costs, health insurers are stampeding to switch patients to drugs that are cheaper to make, test and ultimately buy because their manufacturers can piggyback on the research and marketing already done by brand-name-drug companies. Pharmacists in most states are also free to give patients whichever version of a drug is cheapest for them to supply, without telling the prescribing doctor; in some states, pharmacies are *required* to make this switch. And few of us complain when it happens: Women who wouldn't dream of substituting Diet Pepsi for Diet Coke, simply because of the taste, eagerly swap vital medications, because the change can cut co-pays in half.

Many lawmakers and health-policy experts say the trend has little downside. "Generic drugs have the same active ingredient that brand-name drugs do and are made in FDA-approved plants, just as brand-name drugs are," says Aaron S. Kesselheim, M.D., an instructor in medicine at Harvard Medical School in Boston. In an analysis recently published in *The Journal of the American Medical Association*, Dr. Kesselheim reviewed data from 47 clinical studies and found no evidence that patients on brand-name cardiovascular drugs had clinical outcomes superior to those on generics. Given these results, and the lengths that some brand-name-drug companies have gone to protect their patents and profits, it's easy to believe that any supposed problems with generics are "a story cooked up by Big Pharma"—the conclusion reached by consumer watchdog Peter Lurie, M.D., deputy director of the health-research group at Public Citizen in Washington, D.C.

But a yearlong investigation by SELF—including more than 50 interviews and records leaked from one of the world's largest generic-drug companies, Ranbaxy Laboratories—raises questions about whether some new generics are as safe or effective as the brand names. Although Dr. Kesselheim's review looked at all of the available data, many of those studies were completed before the recent flood of generics hit the market and many generic-drug factories moved overseas. In FDA applications for new generic drugs, nearly 90 percent of the factories providing active ingredients are located overseas, where the agency's inspection rate dropped 57 percent between 2001 and 2008.

"The average citizen would want to know that someone is checking that manufacturers are making the drugs they got approval to make," says William K. Hubbard of Chapel Hill, North Carolina, associate commissioner for policy and planning for the FDA from 1991 to 2005 (and no relation to Beth). "That's not happening, and the risk to consumers is potentially huge. I take generic drugs when they're prescribed for me, but my confidence in them is lower than it was a year ago—and going down."

Generics, which came into widespread use after Congress streamlined testing requirements in 1984, are supposed to be tightly regulated. In the late 1980s, after companies were caught paying off inspectors in order to get generic drugs

approved, the FDA overhauled its rules. The agency vowed to inspect each factory before giving the green light to any application. And it newly required any generic-drug maker seeking approval to make one test lot of the proposed drug and then to produce three larger lots to show its manufacturing capabilities. "I have told the industry they are in charge of the health of the American public," says Gary Buehler, director of the FDA's Office of Generic Drugs, adding, "We have come a long way in how we do inspections."

But SELF found that the FDA's reforms have largely fallen by the wayside. Few applications trigger inspections, according to sources knowledgeable about the process, and instead of the three required lots, companies are making one or none. Manufacturing problems have come to light, with six generic companies recalling 20 products in 2008. KV Pharmaceutical Company, a maker of heart and pain medicine, recalled everything it made. "The FDA is satisfied that generics are OK," says Nada Stotland, M.D., a psychiatrist in Chicago and the president of the American Psychiatric Association. "My question is, Are we satisfied?"

Are generics really the same?

Between 2000 and 2008, the number of new generic drugs put forth for FDA approval went up 40 percent and approvals doubled, with roughly 600 cleared to be sold last year. "Generic companies are popular on Capitol Hill because the industry is powerful and voters are anxious for cheaper drugs. There was always pressure on us to reduce barriers to entry," says Scott Gottlieb, M.D., deputy commissioner for medical and scientific affairs for the FDA from 2005 to 2007. (Dr. Gottlieb is now a resident fellow at the American Enterprise Institute, a conservative think tank in Washington, D.C., and also advises brand-name-drug companies.)

Because brand-name medications have already been clinically tested, generic companies applying for FDA approval don't have to repeat that process on their versions. Instead, they must test their medicine on a minimum of 20 people; subjects take a single dose, so the drug is not tested over time. If tests show the generic contains the same active ingredient that the original does and delivers about the same dose, then the FDA considers it "bioequivalent" and clears it to be sold.

But as Beth Hubbard discovered, patients are finding stark differences among drugs the FDA has deemed equivalent. Pharmacologist Joe Graedon and his wife, Terry, cohosts of the public radio show *The People's Pharmacy*, have fielded complaints about dozens of generics for depression, hypertension, high cholesterol and more. Consumers described drugs that had no effect, caused bizarre side effects or made conditions worse. Joe Graedon says he has been "astounded" by the outpouring. "I'm not in the back pocket of the pharmaceutical companies—I want

generics to be good," he says. "But the more we dug, the more we realized nobody is monitoring the equivalence of these drugs."

After her ordeal, Hubbard hit the Internet. Amazed, she scrolled through hundreds of comments at PeoplesPharmacy.org, many from patients who had switched to the same drug she had—Budeprion XL 300 milligrams, which Impax Laboratories makes and Teva Pharmaceutical Industries distributes. One patient wrote, "I have no history of suicidality, but a day after switching to the generic, I went into a week of steadily rising panic.... I was psychotic, self-loathing way WAY beyond anything I have ever experienced. I made it through the worst of it, called a suicide hotline, took two Ativan and didn't take any more of the Budeprion. The next day I felt much better, and today I'm back to my normal self."

If the drugs were truly bioequivalent, what could account for such divergent reactions? Last fall, the Graedons collaborated with ConsumerLab.com, an independent testing laboratory in White Plains, New York, to find out. Testing revealed that the 300 mg Budeprion XL dose Hubbard had taken dumped four times as much active ingredient during the first two hours as the brand name did. Graedon compares the effect to guzzling alcohol. "If you sip a glass of wine over the course of two or three hours, you're not going to feel drunk," he explains. "But if you drink the whole thing in 15 minutes, you're getting too much too fast."

Release formulas, which control how quickly a drug dissolves in your bloodstream, are something drug companies carefully develop and patent. And these release-formula patents often remain in place after the patent on a drug's active ingredient has expired. That means generic companies must sometimes engineer their own release mechanism, as happened in the case of Budeprion XL. After complaints started rolling in, the FDA concluded in a 2008 report that patients' problems were more likely caused by normal relapses of depression than by differences in the drugs, and Teva stressed that it followed all the FDA's rules. But that report—and the original approval of the 300 mg pill—was based solely on data Teva had submitted for the 150 mg pill; the agency's judgment was that the doses were proportional and would behave similarly in the body. "Neither the FDA nor Teva did the required bioequivalence studies for this pill," counters Tod Cooperman, M.D., president of ConsumerLab.com.

Buehler notes that the FDA won't approve generics that its scientists deem to have "clinically significant" differences in release rates compared to the original. But the bioequivalence studies they base this judgment on aren't public, so doctors and patients have no way of knowing when the FDA has found a difference and how dramatic it is. Nor can they easily find out about differences in fillers and additives, which might change the release rate or in rare cases trigger allergic reactions. "It's scary to think the FDA would approve something it knows is different and still call it equivalent," Dr. Cooperman says.

Some physicians are concerned not only with how fast generics deliver their dose but also about the strength of the dose itself. Because for some drugs, such as those that treat epilepsy and heart disease, even small differences in potency can mean the difference between an ineffective underdose and a toxic overdose.

Stephanie Bornice, a 22-year-old stay-at-home mother of two in Bristol, Pennsylvania, and an epilepsy sufferer since 2002, says she hadn't had a seizure in six years, thanks to the medication Trileptal. But last year, after about a month on the generic, oxcarbazepine, Bornice began to have frightening and familiar symptoms, like tremors before an earthquake. "Someone would be talking, and I wouldn't understand him, or my sight would blur," she remembers. One afternoon, a seizure came on suddenly. She rushed to put her newborn son safely in his crib before, she says, "everything turned black."

Bornice's doctor at the time, Jacqueline French, M.D., professor of neurology at New York University Comprehensive Epilepsy Center in New York City, quickly confirmed Bornice's suspicions that the generic was causing the problem and switched her back. Dr. French describes the case as a "clear-cut failure" of the generic—and not the only one she has seen. "The FDA is telling us that the drugs [dosages] are the same within a certain margin and that should be OK," Dr. French says. "But there are patients holding off seizures by the skin of their teeth."

Ensuring the correct dose becomes even trickier when pharmacists switch customers from one generic version of a drug to another, says John S. Antalis, M.D., a family physician in Dalton, Georgia, who has served on the safe-medication-use committee of U.S. Pharmacopeia, a nonprofit organization in Rockville, Maryland, that sets official standards for all medications. Dr. Antalis cites the dozens of versions of warfarin, the generic for the blood thinner Coumadin. It's a drug that requires patients to have regular blood tests; they risk blood clots if they have too small a dose and internal bleeding if they get too much. It became much harder to monitor the clotting in patients' blood, Dr. Antalis says, because they were being shifted between so many versions of warfarin that it was hard to say which drug was having what effect. "I try to stay on top of any subtle hint of change, but it's difficult," he says.

Physicians' groups, including the American Academy of Neurology in St. Paul, Minnesota; the American Heart Association in Dallas; and the Endocrine Society in Chevy Chase, Maryland—all of whose members prescribe drugs that require delicate dosing—have warned doctors to look out for reactions to generics. They've also called on the FDA to study the issue in more detail. (Many medical societies have ties to brand-name companies; for instance, Abbott Laboratories, maker of the popular brand-name thyroid drug Synthroid, has donated to the American Association of Clinical Endocrinologists in Jacksonville, Florida.)

Some experts chalk up complaints to the fulfillment of expectations: We believe a generic will be worse, so it is. "People hear the word *generic*, and they think about generic cornflakes or plastic wrap," Dr. Kesselheim says. Others dispute that notion. "Patients look forward to having a lower co-pay," says Adam Keller Ashton, M.D., clinical professor of psychiatry at the State University of New York at Buffalo School of Medicine and Biomedical Sciences. (Dr. Ashton says he has earned money from the makers of Wellbutrin in the past but not for the previous two years, and he has no ties to generics.) He estimates that at least 75 of his patients have complained about the 300 mg generic version of Wellbutrin XL. "If it was in their head, why wasn't it in their head when other brands went generic?" he says, adding that many of his patients felt so bad that if he hadn't intervened, "it might have progressed to the point to where lives were in jeopardy."

Dangerous factories

Stephanie T., a 33-year-old in New York City, never gave much thought to where her prescription drugs were manufactured. She knew only that they were helping her get healthy after years of battling schizoaffective disorder. In January 2007, she was productive again, back in school and studying for a degree in medical coding and billing. She had been taking a version of fluoxetine (the generic of Prozac) by a Croatian company, Pliva; then her pharmacy switched her to a fluoxetine made by the Indian generic giant Ranbaxy. Over the next six months, she fell into a deep depression. "I was lying on the couch all day long," recalls Stephanie, who asked SELF not to publish her last name. "I wasn't eating; I couldn't get my schoolwork done. I was crying all the time." If it weren't for her family, she says, "I don't think I'd be around."

Out of the blue, Stephanie's pharmacy switched her back to the medicine made by Pliva. "Within days, I was a brand-new person. I remember lying in bed thinking, What did I do differently?" she says. "When people are mentally ill, changing their drugs is like playing with someone's mind. I could have committed suicide and no one would have known why."

What she could not know was that the government shared her dim view of Ranbaxy's medicine. A criminal investigation of the company had been under way for a year and a half, prompted by employee allegations that its manufacturing efforts were beset with fraud.

In August 2005, a Ranbaxy insider had passed whistle-blowing information to public-health experts in the United States. The papers (obtained by SELF) alleged that Ranbaxy altered testing data, concealed its deviation from safe manufacturing practices and used active pharmaceutical ingredients from unapproved sources. Its customers were taking drugs that were potentially "subpotent, superpotent or adulterated," according to a motion filed by the government in a U.S. District Court

in Maryland last year.

The questionable drugs were being concocted in part for a program launched by George W. Bush called PEPFAR (President's Emergency Plan for AIDS Relief), which sends medicine by the ton to Africa. Officials worried that Ranbaxy had sold dubious AIDS drugs to the taxpayer-funded program. And in the months that followed, evidence would surface that suspect Ranbaxy treatments were reaching Americans, too.

According to hundreds of pages of documents SELF obtained through the Freedom of Information Act, FDA inspectors would eventually find that Ranbaxy delayed telling regulators for months about impurities in its version of the epilepsy drug gabapentin. The company also either failed to report or reported late about complaints from patients taking fluoxetine, generic Accutane and sleeping pills. In an earlier case, the company had not told the FDA about a report from a pregnant woman who took its sleeping pills and had a baby with a birth defect and developmental delays. Ranbaxy admitted the errors and told the FDA they would put procedures in place to prevent them from happening again.

The Ranbaxy scandal is the clearest evidence yet of the FDA's struggle to keep an eye on drug companies that increasingly make their products in India and China. Brand-name drugs are made overseas, too, but globalization has been most dramatic in the generic industry. At recent inspection rates, it would take the FDA 13 years to see every foreign plant once, whereas the agency inspects domestic factories every 2.7 years, according to the U.S. Government Accountability Office. Inspectors generally spend less time on foreign inspections than they do domestically and often must get clearance from foreign governments, which means that companies know they are coming.

Inspections commonly find unsterile work areas or substandard manufacturing practices, former FDA officials say. Yet the agency often relies on paperwork from the plants themselves to determine whether problems have been solved, says Bryan A. Liang, M.D., executive director of the Institute of Health Law Studies at California Western School of Law in San Diego. In many cases, companies can give themselves a clean bill of health. "The FDA does an inspection and rarely goes back," Dr. Liang says. "Anything can happen beyond that point. It's a huge regulatory gap."

Evidence of fraud

Many drugmakers do much more than make drugs: Through its subsidiaries or outsourcing, Ranbaxy handles every stage of the generic-drug-development process, from supplying raw ingredients to testing drugs on volunteers. When a company has so much control over the pipeline, the FDA stands as one of the few checks on drug safety.

Those checks appear to have failed. The whistle-blower documents provided to SELF suggest the company either was dangerously sloppy or outright fraudulent in an essential cornerstone of drug manufacturing known as stability testing. Like a quart of milk in the fridge, drugs can only go bad. The question is how quickly their ingredients degrade; once they break down, the product becomes impure and potentially useless or even hazardous. But Ranbaxy's data showed the incredible: purity levels that never decreased, that improved or that were identical for separate batches, a statistical impossibility. SELF shared the 25 pages of documents with a scientist who has overseen quality assurance for a pharmaceutical manufacturing company; he concluded, "This is either fabricated data, or they don't have people who can even do middle school chemistry."

In one email exchange, a Ranbaxy manager in India notes that data indicating no increase in impurities from 9 to 12 months "will certainly raise doubts, we need to revise this number." And an internal quality review shows that in several instances, the company mixed antiretroviral-drug ingredients for too long a time—which could render them ineffective or toxic. "If you're a regulator and you look at this, that's when you say, 'We're padlocking your front door,'" says the scientist, adding, "If the FDA was in possession of this, it should be putting this medicine on the no-fly list."

The agency had the documents—and was amassing more evidence that the company's products might be dangerous. In February 2006, a year before Stephanie T. grappled with her relapse, the FDA sent inspectors to one of Ranbaxy's plants in India and found serious manufacturing problems. In 2007, federal investigators raided Ranbaxy facilities in New Jersey, seizing documents and computers. An inspection of a second Indian factory in early 2008 found that medicine bound for the United States was improperly handled in a plant that makes penicillin, raising the specter of cross-contamination that could be lethal to people who are allergic. And in its court filing last July, the government alleged that Ranbaxy's violations "continue to result in the introduction of adulterated and misbranded products into interstate commerce."

Yet the agency's only regulatory response to these revelations was to hold off approving applications for drugs manufactured in one of the Indian plants it had inspected. It did not pull the drugs from that factory off the market—or stop approving 39 applications for drugs manufactured at the company's other plants. "The FDA conducted preapproval inspections for only 17 percent of the Ranbaxy applications approved since 2005," reveals Rep. John Dingell, Democrat of Michigan and sponsor of a bill to strengthen the FDA's oversight of food and drug safety. "It also allowed Ranbaxy to perform the key bioequivalence studies in facilities owned by the firm and conducted by clinicians employed by the firm."

A Ranbaxy spokesman, Charles Caprariello, says the company is cooperating fully

with the FDA and the Justice Department and working to resolve authorities' concerns swiftly. He notes that its New Jersey facility is not affected and continues to supply products for U.S. customers, with four new generics approved in 2009. "Ranbaxy remains committed to providing high quality medicines at affordable prices to U.S. patients," he adds.

Last September, three years after learning of the whistle-blower's allegations, the FDA finally issued an "import alert" for Ranbaxy drugs, effectively putting a hold on the importation of more than 30 drugs from two of the company's plants. A draft of the import alert had languished at the agency, a source told SELF, sitting on the desk of an FDA division director before being sent back to a subordinate, where it spent more time.

The agency has now also imposed the rare and serious sanction of scrutinizing all drug-safety data produced by one Indian plant because of its history of falsifications. "We're being very vigorous," says Janet Woodcock, M.D., director of the FDA Center for Drug Evaluation and Research, which oversees drug safety. Dr. Woodcock argues that the FDA's recent actions against generic companies, including Ranbaxy, send a powerful signal that help promote "a culture of accountability around the globe."

Who can protect us?

The goal of low-cost medicine cannot come at the expense of safety. And as Dr. Kesselheim notes, in this bleak economy, generics have become even more important, as the cost of drugs could lead patients to stop taking needed medicine altogether. So how can authorities ensure generic drugs are safe for patients?

For starters, says Dr. Gottlieb, the FDA's Office of Generic Drugs, which controls approvals and inspections, needs more funding. "The FDA can't even keep pace with the inbox, let alone invest in better science," he says. The need will become more acute in coming months, as generic companies push Congress for permission to make delicate, injectable biologic medicines such as Epogen and Neupogen, which are often taken by cancer patients and are more complex to manufacture than traditional pills are.

Doctors are eager to subject highly sensitive drugs that require time- release formulas or precise dosing to more extensive clinical testing, and Graedon would like to see random, off-the-shelf testing of a generic's ingredients and effectiveness after it hits the market. More dynamic oversight would also require equal inspections of brand-name and generic plants, regardless of where they are in the world.

This is beginning to happen. In recent months, the FDA has opened bureaus in China, India, Central America and Europe and plans to expand its presence to

Mexico, South America and the Middle East. Rep. Dingell's bill, the FDA Globalization Act of 2009, would provide funds for further reforms. Still, cautions Dr. Woodcock, "there is no magic point in this process by which you can test everything. Let's say we test 10 tablets and they're making 100,000? The manufacturer is in charge of the quality of the product, and our obligation is to make sure they meet their obligations."

Dr. Stotland, of the American Psychiatric Association, says she remains troubled that most state laws allow pharmacists to change at will from brand names to generics (as well as among different generics). She argues that the law should require them to notify treating physicians of any change. As it stands, doctors who want to ensure their brand-name prescriptions are obeyed must write "Do not substitute" on their prescriptions—which does not guarantee that insurance companies will cover the extra cost. But Charles Mayr, a spokesman for the Generic Pharmaceutical Association in Arlington, Virginia, argues that if pharmacists had the added burden of informing doctors, they would be less likely to dispense generics. "It would help [brand-name] companies preserve monopolies," he says, translating to higher prices for consumers.

In the meantime, patients can help themselves by knowing who made the medications they are taking and noting when their prescriptions change and if they suffer new side effects or a relapse as a result. That's what Beth Hubbard has done. After her eight-month medical odyssey, Hubbard returned to the doctor who first prescribed Wellbutrin and who failed to talk with her about whether her symptoms might be related to a switch to a generic. She doesn't blame him for what happened. Still, she says, "doctors see too many people and they see them too fast, and they don't ask the difficult questions. You have to know your own body and be your own advocate."