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POLITICS

Deadly Medicine

Prescription drugs kill some 200,000 Americans every year. Will that number go up, now that most clinical trials are conducted overseas—on sick Russians, homeless Poles, and slum-dwelling Chinese—in places where regulation is virtually nonexistent, the F.D.A. doesn't reach, and “mistakes” can end up in pauper's graves? The authors investigate the globalization of the pharmaceutical industry, and the U.S. Government's failure to rein in a lethal profit machine.

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TAKE TWO ASPIRIN

More and more clinical trials for new drugs are being outsourced overseas and conducted by companies for hire. Is oversight even possible? *Photographs © Imagebroker/Alamy, from Image Source/Jupiter Images, © Vincent O'Byrne/Alamy (skulls); © Jason Salmon/Alamy (capsule).*

You wouldn't think the cities had much in common. Iași, with a population of 320,000, lies in the Moldavian region of Romania. Mégrine is a town of 24,000 in northern Tunisia, on the Mediterranean Sea. Tartu, Estonia, with a population of 100,000, is the

oldest city in the Baltic States; it is sometimes called “the Athens on the Emajõgi.” Shenyang, in northeastern China, is a major industrial center and transportation hub with a population of 7.2 million.

These places are not on anyone’s Top 10 list of travel destinations. But the advance scouts of the pharmaceutical industry have visited all of them, and scores of similar cities and towns, large and small, in far-flung corners of the planet. They have gone there to find people willing to undergo clinical trials for new drugs, and thereby help persuade the U.S. Food and Drug Administration to declare the drugs safe and effective for Americans. It’s the next big step in globalization, and there’s good reason to wish that it weren’t.

Once upon a time, the drugs Americans took to treat chronic diseases, clear up infections, improve their state of mind, and enhance their sexual vitality were tested primarily either in the United States (the vast majority of cases) or in Europe. No longer. As recently as 1990, according to the inspector general of the Department of Health and Human Services, a mere 271 trials were being conducted in foreign countries of drugs intended for American use. By 2008, the number had risen to 6,485—an increase of more than 2,000 percent. A database being compiled by the National Institutes of Health has identified 58,788 such trials in 173 countries outside the United States since 2000. In 2008 alone, according to the inspector general’s report, 80 percent of the applications submitted to the F.D.A. for new drugs contained data from foreign clinical trials. Increasingly, companies are doing 100 percent of their testing offshore. The inspector general found that the 20 largest U.S.-based pharmaceutical companies now conducted “one-third of their clinical trials exclusively at foreign sites.” All of this is taking place when more drugs than ever—some 2,900 different drugs for some 4,600 different conditions—are undergoing clinical testing and vying to come to market.

Some medical researchers question whether the results of clinical trials conducted in certain other countries are relevant to Americans in the first place. They point out that people in impoverished parts of the world, for a variety of reasons, may metabolize drugs differently from the way Americans do. They note that the prevailing diseases in other countries, such as malaria and tuberculosis, can skew the outcome of clinical trials. But from the point of view of the drug companies, it’s easy to see why moving clinical trials overseas is so appealing. For one thing, it’s cheaper to run trials in places where the local population survives on only a few dollars a day. It’s also easier to recruit patients, who often believe they are being treated for a disease rather than, as may be the case, just getting a placebo as part of an experiment. And it’s easier to find what the industry calls “drug-naïve” patients: people who are not being treated for any disease

and are not currently taking any drugs, and indeed may never have taken any—the sort of people who will almost certainly yield better test results. (For some subjects overseas, participation in a clinical trial may be their first significant exposure to a doctor.) Regulations in many foreign countries are also less stringent, if there are any regulations at all. The risk of litigation is negligible, in some places nonexistent. Ethical concerns are a figure of speech. Finally—a significant plus for the drug companies—the F.D.A. does so little monitoring that the companies can pretty much do and say what they want.

Consent by Thumbprint

Many of today's trials still take place in developed countries, such as Britain, Italy, and Japan. But thousands are taking place in countries with large concentrations of poor, often illiterate people, who in some cases sign consent forms with a thumbprint, or scratch an "X." Bangladesh has been home to 76 clinical trials. There have been clinical trials in Malawi (61), the Russian Federation (1,513), Romania (876), Thailand (786), Ukraine (589), Kazakhstan (15), Peru (494), Iran (292), Turkey (716), and Uganda (132). Throw a dart at a world map and you are unlikely to hit a spot that has escaped the attention of those who scout out locations for the pharmaceutical industry.

The two destinations that one day will eclipse all the others, including Europe and the United States, are China (with 1,861 trials) and India (with 1,457). A few years ago, India was home to more American drug trials than China was, thanks in part to its large English-speaking population. But that has changed. English is now mandatory in China's elementary schools, and, owing to its population edge, China now has more people who speak English than India does.

While Americans may be unfamiliar with the names of foreign cities where clinical trials have been conducted, many of the drugs being tested are staples of their medicine cabinets. One example is Celebrex, a non-steroidal anti-inflammatory drug that has been aggressively promoted in television commercials for a decade. Its manufacturer, Pfizer, the world's largest drug company, has spent more than a billion dollars promoting its use as a pain remedy for arthritis and other conditions, including menstrual cramps. The National Institutes of Health maintains a record of most—but by no means all—drug trials inside and outside the United States. The database counts 290 studies involving Celebrex. Companies are not required to report—and do not report—all studies conducted overseas. According to the database, of the 290 trials for Celebrex, 183 took place in the United States, meaning, one would assume, that 107 took place in other countries. But an informal, country-by-country accounting by *VANITY FAIR* turned up no fewer than 207 Celebrex trials in at least 36 other countries. They ranged

from 1 each in Estonia, Croatia, and Lithuania to 6 each in Costa Rica, Colombia, and Russia, to 8 in Mexico, 9 in China, and 10 in Brazil. But even these numbers understate the extent of the foreign trials. For example, the database lists five Celebrex trials in Ukraine, but just “one” of those trials involved studies in 11 different Ukrainian cities.

The Celebrex story does not have a happy ending. First, it was disclosed that patients taking the drug were more likely to suffer heart attacks and strokes than those who took older and cheaper painkillers. Then it was alleged that Pfizer had suppressed a study calling attention to these very problems. (The company denied that the study was undisclosed and insisted that it “acted responsibly in sharing this information in a timely manner with the F.D.A.”) Soon afterward the *Journal of the Royal Society of Medicine* reported an array of additional negative findings. Meanwhile, Pfizer was promoting Celebrex for use with Alzheimer’s patients, holding out the possibility that the drug would slow the progression of dementia. It didn’t. Sales of Celebrex reached \$3.3 billion in 2004, and then began to quickly drop.

“Rescue Countries”

One big factor in the shift of clinical trials to foreign countries is a loophole in F.D.A. regulations: if studies in the United States suggest that a drug has no benefit, trials from abroad can often be used in their stead to secure F.D.A. approval. There’s even a term for countries that have shown themselves to be especially amenable when drug companies need positive data fast: they’re called “rescue countries.” Rescue countries came to the aid of Ketek, the first of a new generation of widely heralded antibiotics to treat respiratory-tract infections. Ketek was developed in the 1990s by Aventis Pharmaceuticals, now Sanofi-Aventis. In 2004—on April Fools’ Day, as it happens—the F.D.A. certified Ketek as safe and effective. The F.D.A.’s decision was based heavily on the results of studies in Hungary, Morocco, Tunisia, and Turkey.

The approval came less than one month after a researcher in the United States was sentenced to 57 months in prison for falsifying her own Ketek data. Dr. Anne Kirkman-Campbell, of Gadsden, Alabama, seemingly never met a person she couldn’t sign up to participate in a drug trial. She enrolled more than 400 volunteers, about 1 percent of the town’s adult population, including her entire office staff. In return, she collected \$400 a head from Sanofi-Aventis. It later came to light that the data from at least 91 percent of her patients was falsified. (Kirkman-Campbell was not the only troublesome Aventis researcher. Another physician, in charge of the third-largest Ketek trial site, was addicted to cocaine. The same month his data was submitted to the F.D.A. he was arrested while holding his wife hostage at gunpoint.) Nonetheless, on the basis of overseas trials, Ketek won approval.

As the months ticked by, and the number of people taking the drug climbed steadily, the F.D.A. began to get reports of adverse reactions, including serious liver damage that sometimes led to death. The F.D.A.'s leadership remained steadfast in its support of the drug, but criticism by the agency's own researchers eventually leaked out (a very rare occurrence in this close-knit, buttoned-up world). The critics were especially concerned about an ongoing trial in which 4,000 infants and children, some as young as six months, were recruited in more than a dozen countries for an experiment to assess Ketek's effectiveness in treating ear infections and tonsillitis. The trial had been sanctioned over the objections of the F.D.A.'s own reviewers. One of them argued that the trial never should have been allowed to take place—that it was “inappropriate and unethical because it exposed children to harm without evidence of benefits.” In 2006, after inquiries from Congress, the F.D.A. asked Sanofi-Aventis to halt the trial. Less than a year later, one day before the start of a congressional hearing on the F.D.A.'s approval of the drug, the agency suddenly slapped a so-called black-box warning on the label of Ketek, restricting its use. (A black-box warning is the most serious step the F.D.A. can take short of removing a drug from the market.) By then the F.D.A. had received 93 reports of severe adverse reactions to Ketek, resulting in 12 deaths.

During the congressional hearings, lawmakers heard from former F.D.A. scientists who had criticized their agency's oversight of the Ketek trials and the drug-approval process. One was Dr. David Ross, who had been the F.D.A.'s chief reviewer of new drugs for 10 years, and was now the national director of clinical public-health programs for the U.S. Department of Veterans Affairs. When he explained his objections, he offered a litany of reasons that could be applied to any number of other drugs: “Because F.D.A. broke its own rules and allowed Ketek on the market. Because dozens of patients have died or suffered needlessly. Because F.D.A. allowed Ketek's maker to experiment with it on children over reviewers' protests. Because F.D.A. ignored warnings about fraud. And because F.D.A. used data it knew were false to reassure the public about Ketek's safety.”

Trials and Error

To have an effective regulatory system you need a clear chain of command—you need to know who is responsible to whom, all the way up and down the line. There is no effective chain of command in modern American drug testing. Around the time that drugmakers began shifting clinical trials abroad, in the 1990s, they also began to contract out all phases of development and testing, putting them in the hands of for-profit companies. It used to be that clinical trials were done mostly by academic researchers in universities and teaching hospitals, a system that, however imperfect, generally entailed certain minimum standards. The free market has changed all that. Today it is mainly independent contractors who recruit potential patients both in the

U.S. and—increasingly—overseas. They devise the rules for the clinical trials, conduct the trials themselves, prepare reports on the results, ghostwrite technical articles for medical journals, and create promotional campaigns. The people doing the work on the front lines are not independent scientists. They are wage-earning technicians who are paid to gather a certain number of human beings; sometimes sequester and feed them; administer certain chemical inputs; and collect samples of urine and blood at regular intervals. The work looks like agribusiness, not research.

What began as a mom-and-pop operation has grown into a vast army of formal “contract-research organizations” that generate annual revenue of \$20 billion. They can be found conducting trials in every part of the world. By far the largest is Quintiles Transnational, based in Durham, North Carolina. It offers the services of 23,000 employees in 60 countries, and claims that it has “helped develop or commercialize all of the top 30 best-selling drugs.”

Quintiles is privately owned—its investors include two of the U.S.’s top private-equity firms. Other private contractors are public companies, their stock traded on Wall Street. Pharmaceutical Product Development (P.P.D.), a full-service medical contractor based in Wilmington, North Carolina, is a public company with 10,500 employees. It, too, has conducted clinical trials all around the world. In fact, it was involved in the clinical trials for Ketek—a P.P.D. research associate, Ann Marie Cisneros, had been assigned to monitor Dr. Anne Kirkman-Campbell’s testing in Alabama. Cisneros later told the congressional investigating committee that Kirkman-Campbell had indeed engaged in fraud. “But what the court that sentenced her did not know,” Cisneros said, was that “Aventis was not a victim of this fraud.” Cisneros said she had reported her findings of fraud to her employer, P.P.D., and also to Aventis. She told the congressional committee, “What brings me here today is my disbelief at Aventis’s statements that it did not know that fraud was being committed. Mr. Chairman, I knew it, P.P.D. knew it, and Aventis knew it.” Following her testimony the company released a statement saying it regretted the violations that occurred during the study but was not aware of the fraud until after the data was submitted to the F.D.A.

The F.D.A., the federal agency charged with oversight of the food and drugs that Americans consume, is rife with conflicts of interest. Doctors who insist the drug you take is perfectly safe may be collecting hundreds of thousands of dollars from the company selling the drug. (ProPublica, an independent, nonprofit news organization that is compiling an ongoing catalogue of pharmaceutical-company payments to physicians, has identified 17,000 doctors who have collected speaking and consulting fees, including nearly 400 who have received \$100,000 or more since 2009.) Quite often, the F.D.A. never bothers to check for interlocking financial interests. In one

study, the agency failed to document the financial interests of applicants in 31 percent of applications for new-drug approval. Even when the agency or the company knew of a potential conflict of interest, neither acted to guard against bias in the test results.

Because of the deference shown to drug companies by the F.D.A.—and also by Congress, which has failed to impose any meaningful regulation—there is no mandatory public record of the results of drug trials conducted in foreign countries. Nor is there any mandatory public oversight of ongoing trials. If one company were to test an experimental drug that killed more patients than it helped, and kept the results secret, another company might unknowingly repeat the same experiment years later, with the same results. Data is made available to the public on a purely voluntary basis. Its accuracy is unknown. The oversight that does exist often is shot through with the kinds of ethical conflicts that Wall Street would admire. The economic incentives for doctors in poor countries to heed the wishes of the drug companies are immense. An executive at a contract-research organization told the anthropologist Adriana Petryna, author of the book *When Experiments Travel*: “In Russia, a doctor makes two hundred dollars a month, and he is going to make five thousand dollars per Alzheimer’s patient” that he signs up. Even when the most flagrant conflicts are disclosed, penalties are minimal. In truth, the same situation exists in the United States. There’s just more of a chance here, though not a very large one, that adverse outcomes and tainted data will become public. When the pharmaceutical industry insists that its drugs have been tested overseas in accordance with F.D.A. standards, this may be true—but should provide little assurance.

The F.D.A. gets its information on foreign trials almost entirely from the companies themselves. It conducts little or no independent research. The investigators contracted by the pharmaceutical companies to manage clinical trials are left pretty much on their own. In 2008 the F.D.A. inspected just 1.9 percent of trial sites inside the United States to ensure that they were complying with basic standards. Outside the country, it inspected even fewer trial sites—seven-tenths of 1 percent. In 2008, the F.D.A. visited only 45 of the 6,485 locations where foreign drug trials were being conducted.

The pharmaceutical industry dismisses concerns about the reliability of clinical trials conducted in developing countries, but the potential dangers were driven home to Canadian researchers in 2007. While reviewing data from a clinical trial in Iran for a new heart drug, they discovered that many of the results were fraudulent. “It was bad, so bad we thought the data was not salvageable,” Dr. Gordon Guyatt, part of the research group at McMaster University in Hamilton, told Canada’s *National Post*.

In addition to monitoring trials abroad, which it does not really do, the F.D.A. is responsible for inspecting drug-manufacturing plants in other countries, which it also

does not really do. In 2007 and 2008, hundreds of patients taking the blood thinner heparin, which among other purposes is used to prevent blood clots during surgery and dialysis, developed serious allergic reactions as a result of a contaminant introduced at a Chinese manufacturing facility. It took months for the F.D.A., its Chinese counterpart, and Baxter International, the pharmaceutical company that distributed the drug, to track the source of contamination to Changzhou, a city of 3.5 million on the Yangtze River.

The delay was perhaps understandable, given the manufacturing process. The raw material for Baxter's heparin comes from China's many small pig farms. To be precise, it's derived from the mucous membranes of the intestines of slaughtered pigs; the membranes are mixed together and cooked, often in unregulated family workplaces. By the time the source of the contaminant was pinpointed, many more patients in the United States had experienced severe reactions, and as many as 200 had died. It later turned out that the F.D.A. had indeed inspected a Chinese plant—but it was the wrong one. The federal regulators had confused the names.

The good news was that, in this instance, the F.D.A. at least knew which country the heparin had come from. The bad news is that it does not always know where clinical trials are being conducted, or even the names or types of drugs being tested, or the purpose for which they will be prescribed once approved. Companies may withhold the foreign test data until they actually submit the application to the F.D.A. for approval. By then the agency has lost the ability to see whether the trials were managed according to acceptable standards, and whether the data collected was manipulated or fabricated.

\$350 per Child

If the globalization of clinical trials for adult medications has drawn little attention, foreign trials for children's drugs have attracted even less. The Argentinean province of Santiago del Estero, with a population of nearly a million, is one of the country's poorest. In 2008 seven babies participating in drug testing in the province suffered what the U.S. clinical-trials community refers to as "an adverse event": they died. The deaths occurred as the children took part in a medical trial to test the safety of a new vaccine, Synflorix, to prevent pneumonia, ear infections, and other pneumococcal diseases. Developed by GlaxoSmithKline, the world's fourth-largest pharmaceutical company in terms of global prescription-drug sales, the new vaccine was intended to compete against an existing vaccine. In all, at least 14 infants enrolled in clinical trials for the drug died during the testing. Their parents, some illiterate, had their children signed up without understanding that they were taking part in an experiment. Local doctors who persuaded parents to enroll their babies in the trial reportedly received

\$350 per child. The two lead investigators contracted by Glaxo were fined by the Argentinean government. So was Glaxo, though the company maintained that the mortality rate of the children “did not exceed the rate in the regions and countries participating in the study.” No independent group conducted an investigation or performed autopsies. As it happens, the brother of the lead investigator in Santiago del Estero was the Argentinean provincial health minister.

In New Delhi, 49 babies died at the All India Institute of Medical Sciences while taking part in clinical trials over a 30-month period. They were given a variety of new drugs to treat everything from high blood pressure to chronic focal encephalitis, a brain inflammation that causes epileptic seizures and other neurological problems. The blood-pressure drugs had never before been given to anyone under 18. The editor of an Indian medical journal said it was obvious that the trials were intended to extend patent life in Western countries “with no consequence or benefit for India, using Indian children as guinea pigs.” In all, 4,142 children were enrolled in the studies, two-thirds of them less than one year old. But the head of the pediatrics department at the All India Institute maintained that “none of the deaths was due to the medication or interventions used in clinical trials.”

For years, American physicians gave anti-psychotic medicines to children “off label,” meaning that they wrote prescriptions based on testing for adults, sometimes even for different conditions. That didn’t work out so well for the children, who, when it comes to medicine, really are not just little adults. To provide the pharmaceutical industry with an incentive to conduct clinical trials on children’s versions of adult drugs, Congress in 1997 enacted legislation, known as the Pediatric Exclusivity Provision, extending the patent life of certain drugs by six months. It worked so well that the industry has, in the ensuing years, been able to put younger and younger children on more and more drugs, pocketing an extra \$14 billion. Between 1999 and 2007, for instance, the use of anti-psychotic medications on children between the ages of two and five more than doubled.

A study of 174 trials under the Pediatric Exclusivity Provision found that 9 percent of them did not report the location or number of sites of the clinical trials. Of those that did, two-thirds had been conducted in at least one country outside the United States, and 11 percent were conducted entirely outside the United States. Of the 79 trials with more than 100 subjects participating, 87 percent enrolled patients outside the United States. As is the case with adult studies, many children’s trials conducted abroad are neither reported nor catalogued on any publicly accessible government database. There is no public record of their existence or their results.

In the mid-90s, Glaxo conducted clinical trials on the antidepressant Paxil in the United

States, Europe, and South America. Paxil is a member of a class of drugs called selective serotonin re-uptake inhibitors. The class includes Zoloft, Prozac, and Lexapro. In the United Kingdom, Paxil is sold as Seroxat. The clinical trials showed that the drug had no beneficial effect on adolescents; some of the trials indicated that the placebo was more effective than the drug itself. But Glaxo neglected to share this information with consumers; annual sales of the drug had reached \$5 billion in 2003. In an internal document obtained by the *Canadian Medical Association Journal*, the company emphasized how important it was to “effectively manage the dissemination of these data in order to minimize any potential negative commercial impact.” The memo went on to warn that “it would be commercially unacceptable to include a statement that efficacy had not been demonstrated.” After the document was released a Glaxo spokesperson said that the “memo draws an inappropriate conclusion and is not consistent with the facts.”

“Smoke and Mirrors”

It may be just a coincidence, but as controversy swirls around new drugs, and as the F.D.A. continues to slap medicines with new warning labels—especially the black-box warnings that indicate the most serious potential reactions—most of the problematic drugs have all undergone testing outside the United States. Clinical-trial representatives working for GlaxoSmithKline went to Iași, Romania, to test Avandia, a diabetes drug, on the local population. Glaxo representatives also showed up in other cities in Romania—București, Cluj-Napoca, Craiova, and Timișoara—as well as multiple cities in Latvia, Ukraine, Slovakia, the Russian Federation, Poland, Hungary, Lithuania, Estonia, the Czech Republic, Bulgaria, Croatia, Greece, Belgium, the Netherlands, Germany, France, and the United Kingdom. That was for the largest of the Avandia clinical trials. But there have been scores of others, all seeking to prove that the drug is safe and effective. Some took place before the drug was approved by the F.D.A. Others were “post-marketing” studies, done after the fact, as the company cast about for ways to come up with more positive results so it could expand Avandia’s use for other treatments. Based on the initial evaluations, Avandia was expected to—and did—become another Glaxo multi-billion-dollar best-seller.

While sales soared, so, too, did reports of adverse reactions—everything from macular edema to liver injury, from bone fractures to congestive heart failure. In 2009 the Institute for Safe Medication Practices, a Pennsylvania-based nonprofit group that monitors the prescription-drug field, linked the deaths of 1,354 people to Avandia, based on reports filed with the F.D.A. Studies also concluded that people taking the drug had an increased risk of developing heart disease, one of the very conditions that doctors treating diabetics hope to forestall. The risk was so high that worried doctors

inside and outside the F.D.A. sought to have the drug removed from the market, an incredibly difficult task no matter how problematic the medicine. As always, the F.D.A. was late to the party. In 2008 the American Diabetes Association and the European Association for the Study of Diabetes had warned against using Avandia. The Saudi Arabian drug-regulatory agency yanked it from the market, and the Indian government asked Glaxo to halt 19 of its Avandia trials in that country. In September 2010 the European Medicines Agency pulled Avandia from the shelves all across Europe. The F.D.A. still could not bring itself to take decisive action. This even though the F.D.A. knew that Glaxo had withheld critical safety information concerning the increased risk of heart attacks, and the F.D.A. itself had estimated that the drug had caused more than 83,000 heart attacks between 1999 and 2007. The agency settled for imposing new restrictions on the availability of the drug in the United States. Glaxo released a statement saying that it “continues to believe that Avandia is an important treatment for patients with type 2 diabetes,” but that it would “voluntarily cease promotion of Avandia in all the countries in which it operates.”

The Avandia case and others like it have prompted the U.S. Justice Department to mount an investigation under the Foreign Corrupt Practices Act. While it is legal for doctors in this country to accept money from drug companies for acting as consultants, this is not the case abroad, where doctors often are government employees, and such payments can be considered bribes. There are other legal issues. So far, Glaxo has paid out more than \$1 billion to settle lawsuits arising from claims against Avandia and other drugs. The Senate Finance Committee calculates that, since May 2004, seven drug companies have paid out more than \$7 billion in fines and penalties stemming from unlawful drug dealings. Pfizer paid the largest such fine in history—\$2.3 billion for promoting off-label uses of the arthritis drug Bextra.

In theory, pharmaceutical companies are barred from selling a drug for any purpose other than the one that the F.D.A. has approved on the basis of clinical testing. But the reality is different. The minute a drug receives the green light from the F.D.A. for a specific treatment, the sponsoring company and its allies begin campaigns to make it available for other purposes or for other types of patients. The antidepressant Paxil was tested on adults but sold off-label to treat children. Seroquel, an anti-psychotic, was marketed as a treatment for depression. Physicians, often on retainer from pharmaceutical companies, are free to prescribe a drug for any reason if they entertain a belief that it will work. This practice turns the population at large into unwitting guinea pigs whose adverse reactions may go unreported or even unrecognized.

To secure the F.D.A.’s approval for Seroquel, which ultimately would go to treat schizophrenia, bipolar disorders, and manic episodes associated with bipolar disorder,

AstraZeneca, the fifth-largest pharmaceutical company, conducted clinical trials across Asia, Europe, and the United States. Among the sites: Shenyang and more than a dozen other cities in China, and multiple cities in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Croatia, Indonesia, Malaysia, Poland, the Russian Federation, Serbia, Ukraine, and Taiwan. The F.D.A. initially approved the drug for the treatment of schizophrenia. But while schizophrenia may have opened the door, off-label sales opened the cash register. Money poured in by the billions as AstraZeneca promoted the drug for the treatment of any number of other conditions. It was prescribed for children with autism-spectrum disorders and retardation as well as for elderly Alzheimer's patients in nursing homes. The company touted the drug for treatment of aggression, anxiety, anger-management issues, attention-deficit hyperactivity disorder, dementia, and sleeplessness. Up to 70 percent of the prescriptions for Seroquel were written for a purpose other than the one for which it had been approved, and sales rose to more than \$4 billion a year.

It turned out, however, that AstraZeneca had been less than candid about the drug's side effects. One of the most troubling: patients often gained weight and developed diabetes. This meant a new round of drugs to treat conditions caused by Seroquel. In an internal e-mail from 1997 discussing a study comparing Seroquel with an older anti-psychotic drug, Haldol, a company executive praised the work of the project physician, saying she had done a great "smoke-and-mirrors job," which "should minimize (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study." After the e-mail was disclosed, in February 2009, the company said that the document cannot "obscure the fact that AstraZeneca acted responsibly and appropriately as it developed and marketed" the drug. In April, AstraZeneca reached a half-billion-dollar settlement with the federal government over its marketing of Seroquel. The U.S. attorney in Philadelphia, where the settlement was filed, declared that the company had "turned patients into guinea pigs in an unsupervised drug test." Meanwhile, the company was facing more than 25,000 product-liability lawsuits filed by people who contended the drug had caused their diabetes.

Death Toll

The only people who seem to care about the surge of clinical trials in foreign countries are the medical ethicists—not historically a powerhouse when it comes to battling the drug companies. A team of physician-researchers from Duke University, writing last year in the *New England Journal of Medicine*, observed that "this phenomenon raises important questions about the economics and ethics of clinical research and the translation of trial results to clinical practice: Who benefits from the globalization of clinical trials? What is the potential for exploitation of research subjects? Are trial

results accurate and valid, and can they be extrapolated to other settings?" The Duke team noted that, in some places, "financial compensation for research participation may exceed participants' annual wages, and participation in a clinical trial may provide the only access to care" for those taking part in the trial. In 2007, residents of a homeless shelter in Grudziadz, Poland, received as little as \$2 to take part in a flu-vaccine experiment. The subjects thought they were getting a regular flu shot. They were not. At least 20 of them died. The same distorting economic pressures exist for local hospitals or doctors, who may collect hundreds of dollars for every patient they enroll. In theory, a federal institutional review board is supposed to assess every clinical trial, with special concern for the welfare of the human subjects, but this work, too, has now been outsourced to private companies and is often useless. In 2009 the Government Accountability Office conducted a sting operation, winning approval for a clinical trial involving human subjects; the institutional review board failed to discover (if it even tried) that it was dealing with "a bogus company with falsified credentials" and a fake medical device. This was in Los Angeles. If that is oversight in the U.S., imagine what it's like in Kazakhstan or Uganda. Susan Reverby, the Wellesley historian who uncovered the U.S. government's syphilis experiments in Guatemala during the 1940s, was asked in a recent interview to cite any ongoing experimental practices that gave her pause. "Frankly," she said, "I am mostly worried about the drug trials that get done elsewhere now, which we have little control over."

The pharmaceutical industry, needless to say, has a different view. It argues that people participating in a clinical trial may be getting the highest quality of medical care they have ever received. That may be true in the short term. But, unfortunately, the care lasts only until the trial is completed. Many U.S. medical investigators who manage drug trials abroad say they prefer to work overseas, where regulations are lax and "conflict of interest" is a synonym for "business as usual." Inside the United States, doctors who oversee trials are required to fill out forms showing any income they have received from drug companies so as to guard against financial biases in trials. This explains in part why the number of clinical-trial investigators registered with the F.D.A. fell 5.2 percent in the U.S. between 2004 and 2007 while increasing 16 percent in Eastern Europe, 12 percent in Asia, and 10 percent in Latin America. In a recent survey, 70 percent of the eligible U.S. and Western European clinical investigators interviewed said they were discouraged by the current regulatory environment, partly because they are compelled to disclose financial ties to the pharmaceutical industry. In trials conducted outside the United States, few people care.

In 2009, according to the Institute for Safe Medication Practices, 19,551 people died in the United States as a direct result of the prescription drugs they took. That's just the

reported number. It's decidedly low, because it is estimated that only about 10 percent of such deaths are reported. Conservatively, then, the annual American death toll from prescription drugs considered "safe" can be put at around 200,000. That is three times the number of people who die every year from diabetes, four times the number who die from kidney disease. Overall, deaths from F.D.A.-approved prescription drugs dwarf the number of people who die from street drugs such as cocaine and heroin. They dwarf the number who die every year in automobile accidents. So far, these deaths have triggered no medical crusades, no tough new regulations. After a dozen or so deaths linked to runaway Toyotas, Japanese executives were summoned to appear before lawmakers in Washington and were subjected to an onslaught of humiliating publicity. When the pharmaceutical industry meets with lawmakers, it is mainly to provide campaign contributions.

And with more and more of its activities moving overseas, the industry's behavior will become more impenetrable, and more dangerous, than ever.

Keywords

POLITICS, PHARMACEUTICAL INDUSTRY, JANUARY 2011, HEALTH, MEDICINE

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