GLOBALIZATION OF CLINICAL RESEARCH BY THE PHARMACEUTICAL INDUSTRY

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Drug companies' quest for speedy results has led to a boom in trials based in developing countries, where ethical standards may be lax and the impoverished sick abundant. According to the U.S. Department of Health and Human Services Inspector General's office, the number of researchers based outside the United States seeking new drug approvals has increased 16-fold over the last decade. In this article, a 1996 Pfizer trial in Nigeria—the subject of a controversial class-action suit—illustrates the dangers.

By the end of July 2002 a U.S. district court will decide whether drug giant Pfizer should stand trial in the United States for presiding over a coercive, botched 1996 experiment on Nigerian children with meningitis. In a class-action suit filed last August, 30 Nigerian families say the company violated the Nuremberg Code by forcing an unapproved, risky experiment on unwitting subjects who suffered brain damage, loss of hearing, paralysis, and death as a result.

If allowed, the case will open a rare window on a business generally shrouded in U.S. Food and Drug Administration (FDA) and Big Pharma secrecy: the global commerce in human experimentation. Over the past decade, the drug industry has quietly exported its clinical testing overseas, where oversight is slim and patients plentiful. According to a largely unnoticed Health and Human Services (HHS) report, the number of foreign investigators seeking FDA approvals increased 16-fold between 1990 and 1999. The actual numbers are probably much higher—companies aren't required to alert the FDA before taking their research overseas, nor does the FDA track research by location after approving new drugs.

Globalizing clinical research solves the pharmaceutical paradox that while the average American brings home more than ten prescriptions a year, just one in 350 is willing to play guinea pig for new drug testing. An abundance of poor, undertreated, and doctor-trusting patients in Eastern Europe, Latin America, and Southeast Asia renders the quick, positive results corporate sponsors need to get

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new drugs approved fast. According to one review, a whopping 99 percent of controlled trials published in China bestowed positive results upon the treatment under investigation.

Although the HHS report found that the "FDA cannot assure the same level of human subject protections in foreign trials as domestic ones," industry officials say that companies have little interest in bending the rules. "Occasionally things go wrong," allows Pharmaceutical Research and Manufacturers of America official Caroline Loew. But generally speaking, she says, "companies that are investing $800 million in every single drug are not going to waste money on trials that don't meet [the FDA's] exacting standards." Loew says that companies test new drugs abroad so they can sell them to needy foreign patients.

Analysts disagree. "There may be a market" in some developing countries, says Tufts University's drug-development expert Kenneth Kaitin, "but they are really interested in the United States, Europe, and Japan," which dominate more than 80 percent of the global drug market. Indeed, all this foreign experimentation can hardly be counted on to develop malaria vaccines or cure multidrug-resistant TB. "The diseases that are of most interest are mainly the degenerative diseases—arthritis, obesity, heart disease—the diseases of people in the developed world," says South African bioethicist Dr. Solomon Benatar.

Just 0.3 percent of the drug industry's much-touted research and development resulted in the handful of drugs approved for tropical diseases between 1975 and 1997, despite tens of thousands of industry-sponsored clinical trials conducted around the world every year. Currently, U.S. companies are investigating treatments for oral cancer in China, lupus in Mexico, and severe short stature in Eastern Europe, among other studies—not exactly a list of the world's most pressing public health problems.

Even if Americans were willing to participate in trials, they take so many medications that they make poor lab rats anyway, clinical researchers say. To prove a new drug safe and effective, "you want patients with no other disease states and no other treatments. Then you can say relatively clearly that whatever happens to those patients is from the drug," says MDS Pharma's Simon Yaxley, whose company sells what industry public relations folks call "patient recruitment solutions" in Eastern Europe, South Africa, Latin America, and China. In developing countries, many people, because they are poor and don't have access to clinicians and hospitals, aren't taking any medicines for their illnesses.

Not only do experiments on such patients yield clearer results, but recruitment is rapid. "Say you need 1,000 patients in your trial. If you tried Western Europe, it would take you a long time to find untreated patients," Yaxley says. In a developing country, "you might find those patients in half the time." After all,

Editor's note: The author supplies a list of readings at the end of the article.

"the healthcare systems aren't as sophisticated," he adds, and "because of that, there is an increased interest in accessing drugs via clinical research, and therefore we can leverage that interest." Indeed, consumer health advocates say that clinical trials are the only way some poor patients can get any formal healthcare at all.

Government bureaucracy overwhelms clinical research in the United States, scientists complain, but in developing countries "there is tremendous government cooperation," says Kaitin. "The governments of China, India, and Taiwan are bending over backward to get these companies to conduct research and manufacture there. They are giving tax breaks, building facilities. In Taiwan, many hospitals have switched overall record-keeping to English, so if Western companies want to do a clinical trial there, they will have no problem."

Conveniently, many of the FDA's ponderous regulations stop at the border. For example, the FDA's requirement that companies prove that their experimental drugs are safe on animals before starting tests on humans doesn't apply for tests conducted outside the United States. And experiments on Americans must undergo painstaking, lengthy reviews by government-regulated "institutional review boards" (IRBs). But "if you go to some countries and say you want the IRB to review this, they say, 'What is an IRB?'" comments Dennis DeRosia, chair of the Association of Clinical Research Professionals. The FDA simply requires that foreign trials conform to the World Medical Association's Declaration of Helsinki, a series of ethical recommendations that critics call rudimentary, nonbinding, and ambiguous. Scientists routinely ignore Helsinki directives to publish negative results and make study designs public, and they liken Helsinki-required ethics committees in developing countries to rubber stamps. "No ethical questions are raised at all," one investigator admitted to the National Bioethics Advisory Commission (NBAC).

What results is one set of acceptable risks for patients at home and quite another for patients abroad, a double standard that has left hundreds of preventable deaths in its wake. Most notoriously, in the mid- and late 1990s, the National Institutes of Health and the Centers for Disease Control funded and defended studies in which Western scientists withheld treatment from HIV-infected pregnant women in developing countries, even though they knew antiretroviral drugs would reduce the rate of HIV infection in their infants by two-thirds. Hundreds of infants "needlessly contracted HIV infection" while Western doctors presided over their care, according to an incendiary *New England Journal of Medicine* paper by Public Citizen's Dr. Peter Lurie and Dr. Sidney Wolfe.

It wasn't that the lifesaving antiretroviral drugs weren't available to the scientists—the manufacturer offered them free to clinical researchers. Rather, the demands of scientific rigor required that some sick patients go untreated, as NIH and CDC officials explained in a later *NEJM* issue. Only by observing how these untreated patients fared and comparing their outcomes with those of experimental treatments could scientists quickly and decisively determine whether the experimental treatments worked, they wrote. Comparing experimental treatments to

antiretroviral therapy—standard in the West but deemed too expensive, risky, and difficult to administer in poor countries—could only prove whether new treatments equaled or improved upon antiretroviral therapy. But in some cases, "the really relevant question is whether this quick, cheap, easy thing works. You don't really care if the thing works better," explains international-health ethicist Nancy Kass. "What you care about is, does it work, period." Plus, since none of the study subjects could have afforded antiretroviral drugs at the time, NIH's Dr. Harold Varmus and CDC's Dr. David Satcher argued, "the assignment to a placebo group does not carry a risk beyond that associated with standard practice."

Such justifications, retorted former *New England Journal of Medicine* editor Marcia Angell, "are reminiscent of those for the Tuskegee study"—a kind of ethical relativism that results in "widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsoring country."

Government-funded scientists' willingness to sacrifice a few African lives in search of a cheap, effective way to save many more backfired nastily when South African parliamentarian Peter Mokaba recently charged South Africa's new AIDS-treatment programs with foisting dangerous and unnecessary Western drugs upon an unsuspecting African public. According to the *New York Times,* recent revelations of improper conduct in an NIH-funded HIV-transmission trial in Uganda intensified South Africans' receptivity to Mokaba's dangerous accusations. "You set yourself up for these kinds of problems if you don't conduct your study properly," says Lurie. "The researchers have to take responsibility for this."

By all accounts, the quest for rapid results sent Pfizer scientists jetting to Nigeria in late March 1996. Pfizer scientists had been industriously collecting data on its experimental broad-spectrum antibiotic Trovan when one of the worst epidemics of meningococcal meningitis broke out in Nigeria. The scourge presented a golden opportunity to test their hot new drug, which they suspected could effectively treat meningitis in oral form, bypassing the painful injections their competitors' drugs required. "We had to move quickly," a Pfizer spokesperson told the *Washington Post.* In Nigeria, where the contagion infected more than 100,000, the company could test Trovan on hundreds of patients in a matter of weeks.

The Nigerian government was happy to cooperate, arranging for the company's accommodation and silencing criticism from local physicians, according to court documents. The FDA granted permission to export the experimental medicine the very same day it was requested, Pfizer says. And a Nigerian hospital ethics committee sanctioned the study design, as required by Helsinki, the company claims. Not so, confessed two Nigerian doctors to the *Post* in January 2001. "There was no ethical committee at the time of the trial, none met, and no approval was properly given for the trial," said one. The "approval" document was cobbled together long after the experiment concluded and was then backdated, the other doctor said. And Pfizer's study design was dangerously risky, critics say. One of

Pfizer's own scientists, Dr. Juan Walterspiel, warned management that the study methods were "improper and unsafe" before and after the study was conducted, acts of integrity that led to his swift dismissal.

The company, in a heady mix of haste and arrogance, planned to give 100 deathly ill Nigerian children experimental Trovan either orally or by injection, and compare their outcomes to 100 others given shots of competitor Roche's FDA-approved Rocephin. But an oral form of Trovan, though convenient, was too risky to test on dangerously sick poor kids, Walterspiel complained. "Some of the children were in critical condition and most of them malnourished, which made oral absorption even more unpredictable," Walterspiel wrote to Pfizer officials in a December 18, 1997, letter. According to Nigerian families' class-action suit against the company, Pfizer then forced sick children into its study, failing to inform them either of the experimental nature of the drug they'd be subjected to or the availability of WHO-approved meningitis treatment from a nearby Doctors Without Borders team. Not a single Helsinki-required informed-consent form was signed, the company admits. No witnesses signed statements attesting to the "verbal consent" Pfizer claims to have obtained either, the company admits on its website. "These people had no idea they were part of any clinical trial," says Elaine Kusel, an attorney representing the Nigerian families suing Pfizer.

It wasn't the first Third World trial involving lack of consent. One analysis of South African patients who had participated in a study of HIV transmission found that almost 90 percent felt forced into the trial. Thirteen percent of researchers interviewed by NBAC said they weren't sure if their study participants were aware that they were in a research project. "Informed consent is a joke," a clinical investigator who worked in developing countries commented to NBAC. Pfizer scientists took other liberties as well. When some children resisted the painful Rocephin shots, Pfizer scientists slashed the dose to one-third the FDA-approved levels. This unapproved, reckless deviation from the study protocol endangered lives, Kusel charges. Pfizer disputes the claim. The extent of the damage from Trovan and the low dose of Rocephin remains unclear. Pfizer claims it lost just 6 percent of its patients in both the Trovan and Rocephin groups, proving that oral and injected Trovan worked as well as Rocephin. But the company didn't adequately track the long-term recovery of its patients, Kusel says. Initial fatality rates may have been relatively low, but with only one follow-up visit (the FDA recommended two in 1998), nobody knows how many children ended up deaf, brain-damaged, or dead—whether from meningitis, experimental Trovan, or a low dose of Rocephin, she says.

Pfizer defends the study by stressing that the FDA itself found little seriously amiss when it reviewed the data in 1997, a fact maybe more suggestive of the FDA's selective oblivion than Pfizer's propriety. While the agency did decline to consider Pfizer's application, noting "discrepancies," it didn't object to the lack of signed consent forms or note problems with the ethics-approval letter, the company says. The agency's approval of Trovan for no less than 14 adult

indications netted Pfizer more than $160 million until reports of liver damage led the FDA to pull the plug in 1999.

The trial would have remained Pfizer's dirty little secret had the *Washington Post* not unearthed it in a late 2000 investigative series. The sensational, John le Carré–like story of coercive experimentation brought thousands of Nigerians into the streets, launching belated Nigerian and FDA inquiries. In a flurry of outrage, U.S. Representatives Tom Lantos and Henry Hyde sponsored a patient-protection amendment to the Export Administration Act, which would make it more difficult for companies to export experimental medicines abroad.

But Pfizer stands by its study. On its website the company argues that given the impoverished, squalid conditions Pfizer found in Nigeria, patients ought to have deemed themselves lucky to get the cutting-edge medical care and upgraded local facilities that Pfizer's trial offered. "Overall medical care substantially improved due to the presence of this clinical trial," Pfizer says.

This specious argument, that "whatever we do is better than nothing," as Nigerian physician Alphonsus Obayuwana put it, underpins ongoing attempts to rationalize shoddy treatment of poor patients in developing countries. In January 2001, for instance, as part of a trial of a new drug, Discovery Laboratories planned to administer saltwater or air placebos to 325 deathly ill premature infants—arguing that in the poorly equipped Latin American hospitals where the trial would be conducted, patients couldn't afford effective drugs anyway. Discovery admitted to the FDA that its new surfactant drug, called Surfaxin, probably wouldn't improve upon any of the four surfactants the agency had approved since 1990, according to internal FDA documents procured by Public Citizen. But however marginal Surfaxin's contribution to patient care, the drug would be easier to manufacture, the company says. Since the FDA only requires that new drugs prove effective—not more effective than already approved drugs—Discovery planned to seek FDA approval by showing that Surfaxin was better than nothing. The problem of finding parents of dying infants desperate enough to risk being assigned to a placebo group could be overcome by exporting the trial to impoverished Latin American hospitals, "where other drugs in its class are approved, but not standard of care because of financial limitations or government rationing," FDA officials explained in an agency review of the study.

After Public Citizen stepped up pressure, the company redesigned the study without placebos in April 2001, but FDA medical policy associate director Dr. Robert Temple, who participated in an agency review of the study, defends the original study design. "At present nobody in the places where the study would have been done is getting surfactant," he told me. "If they did, the trial half of the people would get surfactant and better perinatal care, and the other half would get better perinatal care. It seems to me all the people in the trial would have been better off." Indeed, Public Citizen's Lurie says, Discovery intended to upgrade research sites to the standards of a Western intensive-care unit—"they just wouldn't squirt active drug down the tube."

The international health advocates one would expect to mount a noisy campaign against shoddy corporate trials have been surprisingly muted. There's a certain wariness about imposing impossible demands and idealistic ethical standards on companies that can easily take their business elsewhere. Doctors Without Borders, the WHO, and other international health organizations have made increasing corporate research interest in the Third World a primary goal, making critiques of such trials secondary, at least for now. "It takes half a second to look at how much more burdened the developing world is with ill health and disability. What we need, if anything, is more health research in the developing world, not less," says Johns Hopkins bioethicist Ruth Faden. Plus, even when companies aim for rich Western consumers, testing new drugs on poor patients "brings benefits to the patients. They get special attention and potential therapy," adds HIV researcher Arthur Ammann, who has tried to convince drug companies to run more trials in developing countries.

Watchdogs like Public Citizen's Health Research Group vociferously decry unethical study designs but can do little to police study conduct, which both the FDA and the drug industry view as secret, "proprietary" information. Ethics documents issued by international associations such as the World Medical Association and the WHO/UNESCO's Council for International Organizations of Medical Sciences, as important as they are, are alarmingly toothless. Pharma companies themselves have attempted a voluntary "harmonization" of clinical research standards abroad to meet FDA standards but, not surprisingly, such efforts are frighteningly nascent in many developing countries.

In the end, such voluntary endeavors, while crucial, are hardly sufficient to protect the would-be guinea pigs of the world sacrificed on the altar of Big Pharma profit. The IRB reviews, FDA approvals, and the like that protect patients at home need to be not only universal but mandatory. With any luck, the class-action suit against Pfizer will strengthen the argument for such protections—at least until the gap between Western elites glutted on the latest medicines and a world majority lacking access to simple antibiotics somehow begins to close.

Note added in proof

The class-action suit against Pfizer was dismissed in the summer of 2002, although it may be refiled in Nigeria.

Note — This article is revised and expanded from "Globalizing Clinical Research," published in *The Nation,* July 1, 2002, pp. 23–28.

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