Drug company trials come under increasing scrutiny

Despite several scandals in recent years, ranging from the death of 11 children in Nigeria to allegations of coverups in the USA resulting in billion-dollar lawsuits, the procedures for monitoring clinical trials by the drug industry remain wanting. Samuel Loewenberg reports.

Last month, three executives from Pfizer were served with arrest warrants in relation to a 1996 clinical trial in which 11 Nigerian children died and scores more suffered debilitating injuries. The warrants are the latest development in an ongoing civil and criminal lawsuit against Pfizer, totalling over US$9 billion.

The lawsuits allege that Pfizer, which was testing an experimental antibiotic treatment for cerebrospinal meningitis called trovafloxacin (Trovan), did not inform the families of the children about the dangers of taking part in the trial, and that the company withheld treatment that could have saved the childrens' lives.

Meanwhile, a US Congressional oversight committee has launched an investigation into how clinical trials are done in the USA and abroad. The committee has begun its inquiry by asking for documents from Schering-Plough Corporation and Merck & Co related to the companies' clinical trial data on cholesterol drugs.

The increased scrutiny of drug testing comes at a precarious time for the embattled pharmaceutical industry. Over the past decade, drug companies have moved around half of their clinical trials to the developing world. With the globalisation of human experimentation, allegations of negligence or malfeasance have been levelled not only against large pharmaceutical companies but also against many well known academic research centres, such as Harvard and Johns Hopkins in the USA.

The controversies highlight the array of ethical questions that arise with doing experiments in low-income countries, including the difficulties of gaining informed consent from illiterate populations, the responsibility to provide medical care for trial participants, and to what extent there is regulatory oversight for trials done overseas.

A report by the Inspector General's Office that oversees the US Food and Drug Administration (FDA) found that some companies specifically went abroad because of lax regulations, and that the FDA does little oversight outside of US borders. Currently, the rules governing human experimentation in the developing world are a patchwork of codes and guidelines from international and national regulators, which patients' advocates and medical ethicists say are easily abused.

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The Pfizer case in Nigeria has received worldwide attention, but with most drug company trials any problems that arise receive scant public scrutiny. "The trials that are being done overseas by drug companies are in a sense secret, because they do not share the information, they cite confidentially, and patient protection", said Tikki Pang, WHO's director of Research Policy and Cooperation. WHO is working to collect data on overseas clinical trials. "Anecdotally, we have heard many, many instances in India, China, and other countries of the possibility of ethical safeguards not being followed", says Pang.

The monitoring agencies in the USA and Europe do have guidelines for overseas trials that all drug companies are supposed to follow. The problem is that the guidelines are for all intents and purposes voluntary. The US National Bioethics Commission, created by former US President Bill Clinton, found in a 2002 report that "ethics-review committees in developing countries were less likely to raise either procedural or substantive issues compared to US boards". Another study in the *Journal of Medical Ethics* found that for trials in developing countries, 25% did not even receive any local official review.

The problem: the FDA relies extensively on review by local

The printed journal includes an image merely for illustration

AP

Anas Mustapha was one of the children involved in Pfizer's experimental meningitis drug trial

Getty Images

Pfizer's trial took place at the Infectious Diseases Hospital in Kano in 1996

researchers. "All we can really do for the most part is look at the written record" to monitor overseas trials, said Robert Temple, director of the FDA's Office of Medical Policy. "The thing I worry about is the quality of consent and the nature of consent. How do you really know what is going on if you are not in there?" Even within the USA, he said, the agency can only inspect a small number of clinical trials. "People may not like this, but it really falls on the responsible investigator", said Temple.

An official from the European Medicines Agency (EMEA), who spoke on the condition that his name would not be used, said that the EMEA also relies on companies to follow the so-called Good Clinical Practice Guidelines, but admitted that there is no oversight by the agency to ensure that the guidelines are followed beyond the companies' own representations. The agency has never refused a marketing application because the guidelines were not followed, he said. "We can enforce how things are done inside of the European Union. We cannot enforce the law within a non-EU country."

In the case of the Nigeria tests, 99 children received a dose of the experimental drug Trovan, while another 101 were given ceftriaxone (Rocephin), a drug already used to treat meningitis. The lawsuits allege that the children given the Rocephin received a dangerously low dose of the drug. The lawsuit further alleges that the parents were barred from the ward, and that all the survivors have lasting disabilities.

According to news reports, Pfizer paid a local investigator US$20 000 (a huge sum for the country) to undertake the study. The investigator has said that he appointed himself chairman of the ethics review committee, and that he fraudulently backdated its approval for the trial. The lawsuit accuses Pfizer of hiding or destroying the data from the trial. "The patients did not know if it was research or not", an unamed Nigerian laboratory technician who took part in the tests told *The Washington Post*. "They just knew they were sick."

Pfizer is fighting the lawsuits and maintains its innocence. "When we did the clinical study in Nigeria, we were following protocols and international standards", said Bryant Haskins, the director of corporate media relations for Pfizer. The firm had not planned on doing a study in Nigeria, he said. It only went in to do the trials because of the epidemic. "We thought we had a drug that would work efficiently in that setting."

The side-effects of Trovan, which included severe liver damage, ultimately caused the EMEA to ban it and the FDA to severely restrict its use. Haskins denies that Pfizer misled the families of the children who were in the trials. "International protocols provide for verbal consent in situations where you are dealing with a population that cannot read or write", he said.

A lawyer for the families of the children who died takes issue with that claim. "Would a civilised nation believe that it is appropriate to conduct experiments on people simply because they nod their head?" asked Peter Safirstein, who is suing Pfizer on behalf of 30 families.

Not only do drug companies do research overseas, they are increasingly hiring out middlemen to do the research for them. These so-called contract research organisations are responsible for finding doctors and other medical professionals and soliciting patients. The contract research industry is now estimated to do $11 billion a year in business, with over 1000 companies hiring out people from Sofia, Bulgaria, to Bangalore, India. "It is the globalisation of human experimentation", said Sidney Wolfe, who heads the Washington, DC based Public Citizen's Health Research Group.

Most drug companies that do overseas clinical trials are seeking high-quality data. But problems regularly arise that the drug companies did not anticipate, said Mark Barnes, who served on a US government committee on human research protections. "My experience is that what often happens, whether it is universities or companies, is that they identify a local investigator who seems qualified, and they think that this person is going to be able to do the study. But [in many developing countries] they do not have the tradition of even keeping medical records, or having qualified staff. In these places you just cannot count on them to sustain a whole complicated clinical protocol over a long period of time." Western companies and universities often "grossly underestimate how complicated it will be for the local researchers to do the study with the standards that we are accustomed to", Barnes told *The Lancet*.

One possible upside to the globalisation of clinical trials is that some standards might increase. Within the UK, the increased risk of litigation has caused companies and medical centres to increasingly follow a US model of heavily regulated trials, said John Porter, who teaches ethics at the London School of Hygiene and Tropical Medicine. UK firms and researchers are "waking up to the issue of litigation, and therefore are setting up increased regulatory systems to make sure they are covered", he said.

Samuel Loewenberg