

Offshore Pharmaceutical Trials: Evidence, Economics, and Ethics

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Backed by a group of wealthy investors and an American university, a US pharmaceutical company recently flouted United States Food and Drug Administration (FDA) safety protections by testing an experimental herpes vaccine offshore.¹ More than 20 American patients with herpes were flown to St Kitts several times to be vaccinated.¹ By participating in a study that was not monitored by the FDA or a safety panel, patients forewent mandated layers of protection against dangerous adverse effects or even death. Indeed, 3 people in whom adverse effects developed after receiving injections of the vaccine took the matter to court in March 2018.² Although the sponsor of the offshore trials downplayed safety concerns and criticized cumbersome FDA regulations, others referred to its research as patently unethical and plainly wrong.

Today, a growing number of American researchers have turned to developing countries to evaluate the safety and effectiveness of drugs in clinical trials.³ A report from the Office of Inspector General of the Department of Health and Human Services found that 80% of approved marketing applications for drugs and biologics contained data from clinical trials conducted outside the United States.⁴ Herein, we analyze this trend, and related concerns and regulations and provide recommendations.

WHY CONDUCT TRIALS OUTSIDE THE UNITED STATES?

Cost is the primary reason for the trend in offshore clinical trials. The average drug requires roughly \$2.6 billion to bring to market, more than half of which is spent on clinical trials.⁵ A first-rate medical center in India charges one-tenth of the fee required by a second-tier American institution.⁶ Speedy recruitment of naive patients and faster completion of trials offshore represent considerable cost savings for pharmaceutical manufactures.

Low- and middle-income countries (LMICs) are often eager to host clinical research.⁷ Many of these nations require clinical trials to use patients from the host country as a prerequisite for regulatory approval or offer intellectual property protections to facilitate drug testing. Foreign governments also impose less regulatory oversight than does the US government. For-profit contract research organizations with extensive foreign connections provide another advantage for offshore testing.

Clinical trials represent an opportunity for LMIC patients who have little or no access to either novel drugs or standard drugs in the United States that are cost-prohibitive locally.⁸ A higher prevalence of certain diseases and lack of exposure to prescription medications make citizens of LMICs ideal, although vulnerable, study participants. Thus, a large pool of potential volunteers, together with lower research costs, facilitate recruitment, reduce time, and lower costs.

CONCERNS: ETHICS AND EVIDENCE OF QUALITY

Ethical treatment of human trial participants, particularly in countries where protections are inadequate, is a significant concern.^{9,10} Pfizer once set up a medical camp in Nigeria to offer treatment to child victims of a bacterial meningitis outbreak while testing its new antibiotic Trovan.¹¹ Many patients were reportedly enrolled without informed consent. Patients and families were not aware that Doctors Without Borders was providing free, proven-effective antibiotics at a medical camp nearby. When Pfizer left Nigeria, it failed to offer long-term follow-up to its human trial participants. Trovan was later discovered to cause a high risk of acute liver failure. This episode illustrates the perils of a lack of effective governmental oversight.

In a study of 33 new products tested in Latin America and approved by the FDA in 2011 and 2012, 21 (80%) of the 26 products

were shown to offer no therapeutic advantage over existing treatments and to have considerable adverse effects.¹² Moreover, many of these drugs were never marketed in the host country or were marketed at prices not affordable to local residents.¹²

Finally, many questioned data validity of offshore testing. The FDA is often unaware of most ongoing foreign studies and receives incomplete information on location and enrollment.⁷ Submitted data frequently come in nonstandard inconsistent formats. Furthermore, some feel that results of foreign trials may not be relevant in treating American patients when they were conducted among patients of different genetic profiles and cultural backgrounds.

LAWS GOVERNING OFFSHORE PHARMACEUTICAL TRIALS

Offshore clinical trials are not completely free of the FDA's regulations. Section 312 of Title 21 of the Code of Federal Regulations requires foreign trials conducted under an Investigational New Device (IND) to comply with all relevant FDA regulations as if they were conducted in the United States. However, under special consideration, the FDA may consider foreign clinical study data to support a marketing approval on its own merit, according to Section 314.106, if the foreign data are applicable to the US population and US medical practice and if the studies have been performed by investigators of recognized competence; the FDA may validate data with on-site inspection if deemed necessary.¹³

Section 312.120 delineates conditions under which these data will be accepted: (1) the study was conducted in accordance with Good Clinical Practice and (2) the FDA can validate the data obtained through on-site inspections.¹⁴ Some feel that these requirements do not sufficiently address safety concerns of foreign clinical trials. In response, a nonbinding 2012 FDA guidance was issued to standardize data submissions from foreign studies and satisfy the requirements of Section 312.120.¹⁵ The guidance recommends submission of a curriculum vitae of investigator qualifications and counsels use of greater details to summarize study protocol and results, and to describe the facility comprehensively. These tweaks, however, are

likely insufficient to protect human participants and improve data quality from foreign trials.

CHALLENGES AND POTENTIAL SOLUTIONS

Greater numbers of offshore clinical trials have increased the foreign data submitted in support of FDA marketing applications.⁷ The FDA is unable to take into consideration all foreign clinical trial information in nonstandard formats. Moreover, even data in standard format are frequently incomplete. The FDA is often unaware of ongoing foreign studies not conducted under an IND. As trials expand to Africa, India, and Latin America, the FDA must visit a growing slate of new offshore sites around the globe.

These developments require the FDA to monitor ongoing trials concurrently, something the agency apparently lacks capacity to do currently. The FDA should encourage sponsors to voluntarily consult with the FDA about proposed foreign trials or to offer incentives for sponsors to submit an IND. The FDA could also require sponsors to submit study information before research begins or require registration of non-IND clinical trials. New legislation to authorize the FDA to expand a database of registration information may also be helpful. At a minimum, the FDA should demand more robust and standardized electronic trial data from sponsors to facilitate "big data" sentinel initiatives for early identification of problem areas. The revised version of ClinicalTrials.gov that controls data quality would further the FDA's mission to safeguard patient rights and safety.

Financial and time constraints permit the FDA to inspect only a very limited number of offshore testing sites; the agency inspected merely .07% of all foreign clinical trial locations compared with 1.9% of all domestic sites.³ Furthermore, inspections of research facilities abroad usually occur after the study is already complete because the FDA is not always aware of trials conducted abroad before their conclusion.

The FDA must optimize its available resources to face this growing challenge. The Office of Inspector General suggested that the FDA could target clinical sites in countries where the FDA had not previously inspected or where Good Clinical Practice standards were only recently adopted.³ Inspections

should occur while foreign studies are ongoing. If expanded registration data were available, the FDA could potentially identify high-risk experiments and target those locations for inspection.

Over the past decade or so, the FDA has partnered with European, Latin American, Middle Eastern, African, Indian, and Chinese counterparts to leverage their resources to monitor clinical trials abroad.⁷ The FDA and its foreign counterparts should continue taking steps toward standardizing ethical oversight of clinical trials globally, perhaps entering multilateral data-sharing agreements. Ultimately, local governments, local regulatory agencies, and ethics committees are responsible for ensuring that their citizens are protected and that the clinical trial data are reliable.

CONCLUSION

As the FDA seeks to address challenges inherent in the globalization of pharmaceutical clinical trials, it should optimize resources, use science-based data standards, and engage in international partnerships. Through these strategies, it will enhance its ability to protect participants and ensure the quality of data obtained from foreign studies, ultimately benefiting consumers in the United States and beyond.

Abbreviations and Acronyms: FDA = Food and Drug Administration; IND = Investigational New Device; LMIC = Low- and middle-income country

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