

Heightened Scrutiny of Foreign Clinical Trials

On June 22, 2010, the US Department of Health and Human Services, Office of Inspector General (HHS-OIG) released a report critical of the US Food and Drug Administration's (FDA's) ability to monitor and inspect foreign clinical trials of drugs and biologics (the Report). The Report's conclusions regarding the extent of foreign trials underlying US applications garnered national media attention.¹ While the Report did not identify any industry lapses in conducting foreign clinical trials or reporting data, the Report's findings are likely to heighten Congressional, FDA and US Department of Justice (DOJ) oversight and enforcement activity. This advisory addresses the risk of increased enforcement action and suggests measures to minimize those risks given that conducting foreign clinical trials is both appropriate and necessary in the global pharmaceutical market.

In addition to increased FDA inspections and monitoring of foreign trial sites, the Report's most serious repercussions may come to companies that have been subject to the recent DOJ Foreign Corrupt Practices Act (FCPA) industry initiative. The Report's conclusions have generated high-level discussion within DOJ about the extent to which payments made by companies and Clinical Research Organizations (CROs) to investigators are being made at fair market value and whether such payments present a threat of corruption with a direct tie to the integrity of data bearing on FDA approval decisions and the safety of US patients.²

OIG Report Overview

The Report concluded that eight percent of marketing applications to the FDA in 2008 relied exclusively on foreign data, 80 percent of approved marketing applications for drugs and biologics relied on at least one foreign clinical study, and 78 percent of all human subjects were enrolled at foreign sites. Because the Office of the Inspector General (OIG) concluded that the number of foreign clinical trials currently being conducted under Investigational New Drug Applications (INDs) has more than doubled in the past decade, it anticipates this trend will continue.

While there are many efficiencies associated with conducting clinical trials abroad, increased reliance upon them comes at a cost unless companies can make sure that

Contacts



Kirk Ogrosky
+1 202.942.5330



Daniel A. Kracov
+1 202.942.5120



Lisa S. Blatt
+1 202.942.5842



Drew A. Harker
+1 202.942.5022



John N. Nassikas
+1 202.942.6820

they, CROs, investigators, and ethics committees comply with applicable laws. As a result of the Report, FDA's increased monitoring and inspection likely will focus on trials in countries with less well developed infrastructure due to perceptions that these countries lack rigorous regulatory oversight capabilities to ensure compliance with good clinical practices (GCPs), including ensuring the ethical treatment of subjects and the integrity of data. To withstand increased scrutiny, companies will want to assess compliance and prepare themselves in advance, focusing on the following questions: (1) are foreign clinical trials, including independent ethics committees and investigator sites, prepared for heightened FDA scrutiny; (2) have companies instituted effective due diligence processes and oversight over third parties such as CROs; and (3) do payments to investigators and other parties involved in trials pass muster under the FCPA, the new UK Bribery Act, and other applicable anticorruption laws?

While FDA can inspect foreign investigator sites for trials under INDs and studies submitted to the Agency, it long has lacked the funding or staffing to conduct many inspections. Strapped for resources, FDA has triaged by selecting inspection sites based on such factors as the risks outlined in protocols, the number of subjects involved, and the investigator's inspection history. Although FDA may inspect while studies are in progress, most trial inspections are conducted only after studies are complete. According to the Report, clinical investigators at domestic sites were 16 times more likely to be inspected than investigators at foreign sites. In addition, OIG noted that 21 percent of subjects were located in countries where FDA conducted no inspections.

The Report also concluded that a key obstacle to FDA's ability to conduct appropriate inspections was its lack of awareness of some ongoing foreign trials. While INDs are required for domestic clinical trials due to the shipment of unapproved products in interstate commerce, they are not required for wholly foreign trials. As a result, FDA may not be informed of a study, its trial protocol, ethical safeguards, or investigators until after the data has been submitted in support of a marketing application.

The Report found that while FDA accepts foreign data from well-designed, well-conducted non-IND studies that has been collected in accordance with GCPs, the Report criticized FDA's ability to track applications and data. While FDA requests that sponsors follow GCPs in submitting study reports and requires sponsors to provide access to underlying raw data, the report found that data reports frequently are submitted in a manner that makes them difficult to analyze, including problems such as incomplete data sets, varied document format, and inconsistent organization.

In response to the Report, FDA is currently working to (1) standardize an electronic format in which data can be submitted; (2) analyze trials not conducted under INDs to determine whether they tend to present added risks; and (3) improve its monitoring of foreign clinical trials including entering into inspection agreements with foreign counterparts, increasing the number of foreign sites inspected under the Bioresearch Monitoring program, and developing new oversight models.

Payments to Foreign Officials a Focus

The Report comes at a sensitive time for the pharmaceutical industry as it is already under the FCPA spotlight.³ FBI agents and federal prosecutors have been examining payments made by companies and their agents to foreign officials to assure that foreign officials are not being corrupted or bribed. The number of third party contracts with CROs, academic and health care facilities, and investigators provides a high-risk area for potential violations. The US government is particularly interested in any corrupt payments that may have wrongfully influenced the reliability or integrity of data emerging from any trial, and companies may find themselves facing critical legal issues if approval of products rested on the results of studies that DOJ deems corrupt.

As a starting point, DOJ has recently taken the public position that many investigators, foreign clinicians, and laboratory workers will be deemed "foreign officials" for purposes of the FCPA.⁴ This is especially true in countries in which major hospitals, clinical laboratories, ethics committees and other healthcare delivery facilities are owned or controlled, in

whole or in part, by a foreign government. “Foreign officials” also could include researchers and medical professionals employed by certain quasi-governmental organizations that receive foreign government funding, such as the World Health Organization. Payments made by companies, or CROs on behalf of companies, to foreign officials may be viewed as action taken to obtain business. Such payments may also endanger the integrity of data collected from site in which corrupt payments have been made, and may hinder the ability for the new drug application (NDA) or biologic license application (BLA) applicants to get FDA approvals. This is certainly the case where corrupt payments may have been used as an incentive to inappropriately increase subject enrollment or where payments to investigators have been inappropriately shared with study subjects in an effort to bolster study numbers. A likely area of scrutiny will be a comparison of the results of FCPA investigations into payments against company disclosures of the financial interests of clinical investigators submitted under 21 C.F.R. Part 54. DOJ also will examine closely differences in payments among investigators in varying locations, and between sites overseen by companies vis-à-vis local CROs. Of course, payments linked to cases of investigator fraud or serious GCP non-compliance will get particular scrutiny. The risks under the FCPA, therefore, may dovetail with risks under the Federal Food, Drug, and Cosmetic Act (FDCA) and other US laws in certain circumstances.

Alien Tort Claims Act

In addition to the Report and the FCPA Pharmaceutical Initiative, on June 29, 2010, the US Supreme Court denied Pfizer’s petition for a *writ of certiorari* in *Pfizer, Inc. v. Abdullahi, Rabi, et al.*⁵ Pfizer had argued that the Second Circuit impermissibly expanded the scope of the Alien Tort Claims Act.⁶ The Court’s denial sets the stage to allow the plaintiffs to go forward with claims relating a clinical trial involving the study of the antibiotic Trovan® (trovafloxacin) in a 1996 meningitis outbreak in Nigeria.⁷ This litigation, involving allegations of wrongdoing that Pfizer strongly disputes, undoubtedly will draw further plaintiffs’ bar attention to foreign clinical trials.

How to Respond

Given the current environment, companies should conduct risk assessments and audits to avoid potential FDCA and FCPA liability in relation to foreign clinical trials. In particular, US pharmaceutical and medical device companies are expected to engage in meaningful due diligence on trial sites, individual investigators, independent ethics committees, and third-party intermediaries, such as CROs. US companies must also assure that contractual relationships with CROs, investigators and others involved in conducting trials conform to fair market value and other standards and that individual site compliance is monitored. A failure to ensure adequate diligence on and compliance by investigators, CROs, and trial sites can lead to dire consequences for both companies and individuals for FCPA violations, as well as invalidation of study results and potential civil and criminal actions for fraudulent activities. Ignorance may afford no defense, as the FCPA imposes an affirmative duty on supervising entities to ensure FCPA compliance by their agents, including third party contractors, and there is strict liability for misdemeanor violations of the FDCA. Such actions could extend to company executives in a responsible relation to clinical operations intended to ensure compliance.

To assure effective alignment of global compliance in the foreign clinical trial arena, companies should be focused on third-party due diligence, FCPA compliant contracts with fair market value assessments, avoiding suspicious payment structures, careful design of foreign trials, monitoring and quality assurance plans to reduce corruption and GCP non-compliance risks, implementing comprehensive compliance programs, and continuous monitoring of third party performance. A particular area of focus should be ensuring coordination and cooperation of global clinical operations/ quality assurance and general corporate compliance operations, which for many companies are operated separately, leading to potential gaps or inefficiencies in compliance oversight. Where third-party contractors are government or state owned entities, a broadly defined term under the FCPA and in many jurisdictions, companies must take extra care to ensure that the terms of the engagement are clear, transparent, and reflect a fair market value

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exchange in an arm's length transaction. A guiding principle is demonstrating the absence of any corrupt motive.

Conclusion

Given the likelihood that foreign clinical trials will garner significantly more government and public attention in the wake of the Report, the FCPA Initiative, and the *Trovan* litigation, pharmaceutical and medical device companies must reevaluate their approach conducting foreign clinical trials. To mitigate potential liabilities before the government comes calling, companies should consider a careful assessment and remediation of areas of exposure, with particular attention to the rigor of monitoring and auditing plans for foreign trials, the risks inherent in engaging third parties such as CROs to undertake trials, as well as interactions with HCPs who in many countries may be considered government officials under the FCPA.

(Endnotes)

- 1 Office of Inspector General, Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials (June 2010) available at <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>.
- 2 Arnold & Porter LLP attorneys have been counseling companies on FCPA risk in the clinical trial arena for several years. "The Foreign Corrupt Practices Act and Clinical Trials: A Trap for the Unwary." *Food and Drug Law Journal*; Volume 63, Issue 2. *FDLI*. 2008, available at http://www.arnoldporter.com/public_document.cfm?id=12062&key=17C2.
- 3 See Lanny A. Breuer, Assistant Attorney General, US Dep't of Just., Crim. Div., Prepared Keynote Address to The Tenth Annual Pharmaceutical Regulatory and Compliance Congress and Best Practices Forum (November 12, 2009), available at <http://www.justice.gov/criminal/pr/speeches-testimony/documents/11-12-09breuer-pharmaspeech.pdf>.
- 4 See, e.g., *Id.* ("In some foreign countries and under certain circumstances, nearly every aspect of the approval manufacture, import, export, pricing, sale and marketing of a drug may involve a 'foreign official' within the meaning of the FCPA.").
- 5 No. 09-34, 2010 WL 2571888 (U.S. June 29, 2010)
- 6 See Petition for Writ of Certiorari, *Pfizer v. Abdullahi, Rabi, et al.*, No. 09-74 (U.S. June 29, 2010).
- 7 *Abdullahi, Rabi, et al. v. Pfizer*, 562 F.3d 163, 170-71 (2d. Cir. 2009). The plaintiffs assert that the clinical trial involved the administration of Trovan to children without advising them or their guardians of the risks and without obtaining consent, allegations which Pfizer strongly disputes.

We hope that you have found this advisory useful. If you have additional questions, please contact your Arnold & Porter attorney or:

Kirk Ogrosky
+1 202.942.5330
Kirk.Ogrosky@aporter.com

Daniel A. Kracov
+1 202.942.5120
Daniel.Kracov@aporter.com

Lisa S. Blatt
+1 202.942.5842
Lisa.Blatt@aporter.com

Drew A. Harker
+1 202.942.5022
Drew.Harker@aporter.com

John N. Nassikas
+1 202.942.6820
John.Nassikas@aporter.com

Keith M. Korenchuk
+1 202.942.5817
Keith.Korenchuk@aporter.com

Marcus A. Asner
+1 212.715.1789
Marcus.Asner@aporter.com

Mahnu V. Davar
+1 202.942.6172
Mahnu.Davar@aporter.com

Holly C. Barker*
+1 202.942.6793
Holly.Barker@aporter.com

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