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Preparing for Heightened Scrutiny of Global Clinical Trials

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Many pharmaceutical and medical device companies preparing for the Department of Justice's ongoing Foreign Corrupt Practices Act (FCPA) initiative have focused on the risks associated with product marketing, distribution and procurement. While these areas are important, global clinical trials are a source of equal, if not greater, regulatory and anti-corruption law risk. The U.S. Department of Health and Human Services, Office of Inspector General (OIG) highlighted these issues in a June 22, 2010 report that was critical of FDA's ability to monitor and inspect foreign clinical trials of drugs and biologics.[1] The Report's conclusions regarding the extent of foreign trials underlying U.S. applications garnered national media attention.

While the Report did not identify any specific industry lapses in conducting foreign clinical trials or reporting data, its findings are likely to have a significant impact on FDA, US Department of Justice (DOJ) and congressional priorities. In addition to increased FDA inspections and monitoring of foreign trial sites, the Report's conclusions have reportedly generated high-level discussion within DOJ about the extent to which payments made by companies and Clinical Research Organizations (CROs) to investigators and research institutions 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 U.S. patients.

While there are many reasons to conduct global clinical trials, increased reliance upon them comes at a cost unless companies can make sure that their employees, CROs, investigators, and trial partners comply with applicable laws. To withstand increased scrutiny, companies will want to assess compliance and prepare themselves in advance, including fully addressing the following questions:

1. Have you instituted effective due diligence, monitoring, auditing and compliance investigation processes, both in internal R&D/clinical operations functions and with respect to third parties such as CROs and sites? Are these efforts well-coordinated with other compliance functions?
2. Are current foreign clinical trial partners and participants, such as independent ethics committees, research institutions and investigators, prepared for heightened scrutiny in terms of the integrity of their own policies and procedures?
3. Do payments to investigators and other parties involved in trials pass muster under the FCPA, the new UK Bribery Act, and other applicable anti-corruption laws?

OIG Report Overview

The OIG report found striking trends in the internationalization of clinical research supporting

FDA applications: 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 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 anticipated that this trend will continue.

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 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 also found that while FDA accepts foreign data from well-designed, well-conducted non-IND studies collected in accordance with GCPs, the OIG 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 pharmaceutical and medical device industries already under the FCPA spotlight. 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, and DOJ has a particular interest in any corrupt payments that may have wrongfully influenced the reliability or integrity of data emerging from any trial.

As a starting point, DOJ indicated that it will consider many investigators, foreign clinicians, and laboratory workers "foreign officials" for purposes of the FCPA. 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 a site in which corrupt payments have been made, and may hinder the ability for the new drug application (NDA) or biologic license application (BLA) to get FDA approval. 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.

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, U.S. 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. U.S. 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 effectively 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 in many companies operate relatively independently, 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 exchange in an arm's length transaction. A guiding principle is demonstrating the absence of any corrupt motive.

Given the likelihood that foreign clinical trials will garner significantly more government and public attention, pharmaceutical and medical device companies must reevaluate their approach conducting global 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.

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[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.