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Clinical trials and anti-corruption laws: Managing risk in a rapidly changing environment

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The life sciences industry has long been a focus of anti-corruption enforcement, and changing models for global clinical research have made anti-corruption a critical risk area for research-based pharmaceutical and medical device companies.

As of January 2019, 48% of all clinical trials registered with the US National Institutes of Health occurred outside of the United States.[1] Because of an increasingly transnational footprint and the significant level of governmental interactions (e.g., government-owned hospitals, national tenders for medical supplies), the life sciences industry is especially susceptible to the risk of liability under anti-corruption laws.

Given recent anti-corruption enforcement trends, increased multi-jurisdictional cooperation between enforcement authorities, and the specific interest of regulators in the life sciences industry, it is critically important that companies pursue comprehensive risk analysis and mitigation efforts.

ANTI-CORRUPTION ENFORCEMENT

In 2009, the United States Department of Justice (DOJ) declared that it would be "intensely focused on rooting out foreign bribery in [the pharmaceutical and biotech industry]."[2] Over the next decade, the DOJ and the Securities and Exchange Commission (SEC) resolved 22 Foreign Corrupt Practices Act (FCPA) enforcement actions against life sciences companies, imposing more than $300 million in penalties. This focus has continued with recent settlements by Zimmer-Biomet and Stryker.

FCPA enforcement continued at a steady pace in 2017 and 2018. The DOJ brought a total of seven corporate criminal enforcement actions across all industries, including three major investigations conducted in cooperation with foreign enforcement authorities:

- Telia agreed to pay a total of $965 million to the United States,[3] the Netherlands, and Sweden;
- Keppel Offshore agreed to pay more than $422 million to the United States, Singapore, and Brazil; and
- SBM Offshore agreed to pay $238 million to the United States in addition to the $240 million it paid Dutch authorities and additional penalties it is likely to pay Brazil.

All told, in 2017, the US brought in $822 million in corporate criminal fines, penalties, and forfeitures. On the civil side, the SEC resolved a range of FCPA charges in 2017, including $6 million in disgorgement and penalties by Orthofix International for illegal payments to doctors at government-owned hospitals in Brazil, and $13 million from Alere Inc. to settle charges that its subsidiaries bribed foreign officials to make sales of its diagnostic test products and committed accounting fraud in India and Colombia.

In a November 2018 speech, Deputy Attorney General Rod Rosenstein noted that "[f]ighting white collar crime is a top priority for the Department, and we increased prosecutions in every priority area last year. Thanks to a series of initiatives and policy enhancements, we are making white collar enforcement more effective and more efficient."[4]

In 2018, there were six DOJ corporate FCPA enforcement actions, totaling more than $597 million in settlement resolutions. The SEC closed twelve enforcement actions over the same period, including a $7.8 million penalty assessed against Stryker Corporation, a Michigan-based medical device company, for insufficient internal accounting controls and inaccurate books and records.

To date, we are aware of eleven publicly disclosed FCPA investigations open against life sciences companies, with potentially more undisclosed.

Life sciences companies with a global presence must also consider the enforcement of other anti-corruption laws. The new leadership of the UK's Serious Fraud Office is emphasizing increased international collaboration in their enforcement of the UK Bribery Act, as well as encouraging companies under investigation to cooperate with authorities.

In January 2018, Israeli authorities fined Teva Pharmaceutical $22 million for paying bribes in Russia, Ukraine, and Mexico to increase sales. Chinese authorities remained aggressive in their

enforcement of administrative and criminal regulations against commercial bribery.

ANTI-CORRUPTION RISKS IN CLINICAL TRIALS

Most companies understand the anti-corruption risks associated with international sales and marketing activities, and have compliance programs in place to deal with commonplace risks. However, many companies have not fully expanded their anti-corruption compliance programs to cover the unique risks of the clinical research and development (R&D) area.

Clinical trials present their own unique anti-corruption compliance challenges. Companies conducting clinical trials abroad face particular exposure because of the presence of foreign officials at nearly every stage of the process.

In addition to the risks at the regulatory approval phase, companies must also monitor any payments made in connection with the clinical trial, as the healthcare professionals (HCPs) receiving these payments may be considered foreign officials under the FCPA and other anti-corruption laws.

For example, many investigators are employed by healthcare institutions which are owned in whole or in part by government authorities. Clinical investigational product supply often must flow through government-licensed distribution agents.

Clinical laboratory services and other ancillary services necessary to conduct research may be owned or controlled by government officials, their business interests, or, in some cases, their families. Similarly, ethics committees — which play a key role in approving and overseeing clinical trials — may be comprised of government officials.

The second EU study on corruption in the healthcare sector found that corruption risk remained significant in Eastern and Southern Member States, including corruption in clinical trials.[5]

While there are many efficiencies associated with conducting clinical trials abroad, reliance on global trials requires companies to ensure that the Clinical Research Organizations (CROs), investigators, and ethics committees comply with applicable laws. CROs are the classic "third-party intermediary," interacting with government officials and health care professionals to obtain valuable data and regulatory approvals.

Enforcement risk is especially high in countries with less well-developed infrastructure due to perceptions that these countries lack rigorous regulatory oversight capabilities and where companies, often lacking in-country expertise or resources, rely heavily or exclusively on third-party CROs. To withstand this increased scrutiny, companies should assess their clinical trial vendors' compliance and prepare themselves in advance.

Some key questions to consider include:

- Are your partners in global clinical trials, including CROs, independent ethics committees and investigator sites, prepared for heightened scrutiny in this area, and do they understand the consequences of violating anti-corruption laws?;
- Have you and your partners instituted effective due diligence processes and oversight over third parties involved in your clinical research plans?;
- Do planned payments to investigators, hospitals, and other parties involved in clinical trials and R&D pass muster under the FCPA, the UK Bribery Act, and other anti-corruption laws?; and
- Are there other local regulatory regimes covering payments to healthcare professionals, employees of state-owned enterprises and/or government officials?

Payments to CROs, academic and healthcare facilities, and investigators represent a higher risk area for potential anti-corruption violations, and these risks may dovetail with risks under the US Federal Food, Drug, and Cosmetic Act (FDCA), or equivalent laws in other jurisdictions.

Regulatory approval authorities, such as the United States Food & Drug Administration (FDA), the European Medicines Agency, and the China National Medical Products Administration, focus on factors that may influence the reliability or integrity of data emerging from clinical trials, and companies may find themselves facing critical legal issues if product approvals are obtained based on potentially compromised data from studies that authorities deem corrupt.

Payments made by companies, or by CROs on behalf of companies, to ex-U.S. healthcare professionals (HCPs) may be viewed as efforts to influence the actions of those HCPs in an effort to gain a business advantage, raising concerns under anti-corruption laws.

Such payments may also endanger the integrity of data collected from the clinical trial site, hinder the ability of the clinical trial sponsor to obtain product marketing authorizations, and violate not only anti-corruption laws, but also regulations designed to ensure the quality of clinical studies, such as Good Laboratory Practice (GLP) and Good Clinical Practice regulations (GCP).

This is certainly the case where payments may have been used as an incentive to inappropriately increase subject enrollment, influence subjective elements in a trial (such as case report form completion or data interpretation) or where payments to investigators have been inappropriately shared with study subjects in an effort to bolster enrollment numbers.

For example, the FDA attempts to manage financial conflicts of interest by requiring review by Institutional Review Boards or Ethics Committees as well as disclosure of financial conflicts in drug, biologic, and device approval applications.[6] EU legislation also requires that financial information should be documented and available for review by ethics committees.[7]

Other authorities such as the DOJ or the SEC are more likely to take the lead on investigating the corruption aspects of problematic payment relationships with foreign officials, though they could coordinate with the FDA for its subject matter expertise. The DOJ is also likely to examine differences in payments among investigators in varying locations, and between sites overseen by companies vis-à-vis local CROs.

Furthermore, discovery of a significant financial conflict could prompt the FDA to pursue its own inquiry into the integrity of the data collected by sites or CROs implicated in such misconduct, and to censor data or reject applications.

HOW TO RESPOND

Given the current environment, companies should conduct risk assessments and audits to avoid potential liability from foreign clinical trials. In particular, pharmaceutical and medical device companies are expected to engage in meaningful due diligence of trial sites, individual investigators, independent ethics committees, and CROs and other agents and third-party intermediaries.

Companies must also ensure that payments to CROs, investigators and others involved in conducting clinical trials conform to fair market value and monitor their activities to ensure the compliance of all parties involved.

While it is always a challenge to balance the need for speed in a study with quality and compliance, front-end diligence on CROs and sites can set enforceable expectations about company policies and ethics that create a good record in the event of an anti-corruption investigation or data integrity crisis.

A failure to perform risk-based diligence and subsequent monitoring can imperil the reputation of a company and its partners as well as invalidate some or all of the data in a clinical study.

Moreover, recent DOJ guidance indicates that companies that voluntarily self-disclose, fully cooperate with the DOJ's investigation, and timely and appropriately remediate, will receive a presumption of non-prosecution.[8]

This creates an incentive for pharmaceutical and medical device companies to revisit their R&D compliance programs — including their CRO and other third-party due diligence and monitoring programs — to ensure that their mechanisms for preventing, detecting and correcting violations are up to date.

Risk-based clinical trial site monitoring — already a norm in the GLP and GCP world — creates an existing vehicle on which companies can add monitoring processes for invoicing, proof of service, subcontracting or delegation of authority oversight, and supplier diligence, and other measures.

A particular area of focus should be ensuring coordination of global clinical operations and quality assurance with general corporate compliance; for many companies these first two sectors are operated in a manner that is largely independent from general compliance, leading to potential gaps in compliance oversight.

Government-affiliated or state-owned consultants and vendors are a particular risk area, given their critical role in the clinical trial process and the potentially high-value monetary payments involved in their work.

Transparency is also key. As noted above, legislation in the US and EU requires transparency and review of financial information. Furthermore, sunshine rules in the EU also include transfers of value in the context of research and development, although such payments can be disclosed in aggregate. Compliance with these sunshine laws helps to demonstrate a culture of compliance within the company.

CONCLUSION

Many companies focus their anti-bribery and anti-corruption controls on post-approval sales and marketing activities, but often fail to adequately consider the resources needed to manage the unique corruption risks in research and development. There is no safe harbor for research activity under global anti-corruption laws. Given the importance of laboratory research and clinical trials to support marketing applications, senior leaders, general counsels, and chief compliance officers should invest in their companies' global R&D compliance programs accordingly.

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 clinical

trials, the risks inherent in engaging third parties such as CROs to undertake trials, and the related interactions with HCPs and government officials.

NOTES

[1] U.S. National Institutes of Health, ClinicalTrials.gov, Trends, Charts, & Maps (last visited January 16, 2019), https://bit.ly/1GpVrnb.

[2] *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 https://bit.ly/2BilOjK.

[3] Including payments to both the DOJ and SEC.

[4] *See* Rod J. Rosenstein, Deputy Attorney General, US Dep't of Just., Prepared Remarks to the American Conference Institute's 35th International Conference on the Foreign Corrupt Practices Act (November 29, 2018), *available at* https://bit.ly/2QziGJn.

[5] Updated Study on Corruption in the Healthcare Sector, European Commission (September 2017), *available at* https://bit.ly/2hZ5A8o.

[6] *See* 21 C.F.R. Part 54.

[7] *See* Article 6 Directive 2001/20/EC.

[8] *See* U.S. Dep't of Justice, Justice Manual § 9-47.120 (2019).

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