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Beyond Bribery And Corruption: Enforcement Trends In Global Healthcare Compliance

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Lincoln Tsang, Silvia Valverde and Jacqueline Mulryne explore how healthcare product companies are increasingly coming under the scrutiny of regulators worldwide.

In the highly regulated and increasingly globalized life sciences and healthcare sector, industry compliance goes beyond just meeting rules against bribery and corruption.

There is evidence of increased scrutiny by the regulators in a number of areas affecting the entire product life-cycle, and of greater cooperation amongst authorities around the world. Compliance is therefore no longer focused on inducements but on broader business conduct to ensure best practices and governance.

This article discusses the trend for increased global scrutiny of the industry, focusing on some key areas that have been the subject of greater vigilance and enforcement activities.

Compliance: A Multi-Disciplinary And Cross-Border Pursuit

Globalization is a phenomenon where people and countries are increasingly inter-connected and inter-dependent, thanks to the technological advances that facilitate greater cross-border economic activity. For the life sciences and healthcare sector, challenges associated with globalization have led to greater demand for coordination by regulators around the world and the supervision of all stages relating to the research, development and commercialization of products. As a result, compliance is becoming a multi-disciplinary and cross-border pursuit affecting all areas of a company's business, especially as emerging markets become important business targets for growth, and with the potential to reduce costs of development and manufacture.

In many countries, the government is a primary payer for managing healthcare delivery and adoption of new technologies. Greater interest is now being placed on detecting, investigating and enforcing findings of business misconduct: combating bribery and corruption has been a key focus for the authorities. The need to establish legal instruments to support compliance and address corruption at an international level has been recognized by certain key international bodies, such as the United Nations and the Organisation for Economic Co-operation and Development, for decades. In addition, recent prosecutions of multinational pharmaceutical companies highlight the importance of healthcare compliance for international corporations.

For more than a decade, the US Department of Justice has taken an aggressive enforcement stance towards the life sciences industry, which has resulted in billions of dollars in fines and penalties, criminal liability and follow-on litigation. These cases have attracted international attention, and have prompted law enforcement authorities around the world to increase their own scrutiny of the healthcare industry.

However, there is still a long way to go. Global anti-corruption organisation Transparency International recently published a report on corruption in the pharmaceutical sector, identifying key policy and structural issues in selected activities of the pharmaceutical chain, along with corresponding anti-corruption measures¹. The report highlights the lack of objective data and understanding of corruption, the weak legislative framework in some countries, the potential for undue influence from companies, and the lack of leadership committed to anti-corruption efforts as the four overarching challenges faced by the sector.

In Europe, the challenge of corruption is high on the agenda of the European Commission, which estimates that

corruption costs the European economy around €120bn per year². EU member states have taken many initiatives in recent years, including general anti-bribery laws and sector-specific regulations, with inconsistent results.

Increased Scrutiny And Cross-Border Collaboration

To respond to the challenges of an increasingly globalized industry, regulatory authorities have increased cooperation and information-sharing. Bribery is still a key area of activity. At an international level, the UN Convention Against Corruption and the OECD instruments to combat bribery, including the Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, are a result of such increased cooperation.

In addition, it is generally recognized that whistle-blowing is an effective way of exposing misconduct and bad business practices. Over the past 20 years, new whistle-blower laws and policies have been developed throughout the world to enhance compliance oversight. Backed by public support, meaningful opportunities have opened to grant whistle-blowers greater protection, and this will have a significant practical impact on industry practices.

Greater cooperation amongst regulatory and enforcement authorities also heightens the risks of cross-border enforcement and prosecution. In April 2011, Johnson & Johnson agreed to pay a total of US\$78m in settlement agreements with the US DOJ, the US Securities and Exchange Commission, and the UK's Serious Fraud Office in connection with payments allegedly made to doctors and hospital administrators in Greece, Poland, and Romania, as well as asserted kickbacks under the UN's Oil for Food Program in Iraq.

Similarly, the 2014 criminal investigation of GlaxoSmith-Kline³, in which the UK Serious Fraud Office and the Chinese authorities cooperated for the first time, triggered further investigations on interactions with healthcare professionals in Poland, Iraq, Jordan and Lebanon.

In September 2014, a number of regulatory agencies, including the European Medicines Agency and the US Food and Drug Administration, joined the International Coalition of Medicines Regulatory Authorities, which acts as a forum to support international cooperation among medicines regulatory authorities. There are also a number of agreements between the EMA and FDA specifically (as well as other authorities around the

world), such as confidentiality arrangements that seek to facilitate exchange of confidential information as part of their regulatory and scientific processes⁴. These arrangements cover information on advanced drafts of legislation and regulatory guidance documents, and non-public information related to ensuring the quality, safety and efficacy of medicinal products.

The implication of this cooperation is that a breach in one country will most likely be shared with regulators in other countries, leading to increased cross-border exposure to legal risks in the event of non-compliance. Therefore, compliance should not be viewed as a tangible or intangible burden on the business; rather, it should be considered as a necessity and a corporate responsibility.

Inspections

The complexity of the supply chain, often involving third parties, and the novel technology used, have led to an increase in the number of regulatory inspections drug manufacturers undergo worldwide. These inspections have not only changed in frequency, but also in focus.

Companies are being chosen for inspections based on a determination of risks. For example, the FDA's risk-based inspection model grants certain concession to companies with good track-records.

The FDA and the EMA both take into account risk factors, including levels of recalls and adverse events, together with compliance history in applying a risk-based approach⁵. In 2014, the FDA decided to cut back – by nearly 40% – its routine quality inspections in the US in favor of concentrating on more inspections overseas⁶. The agency's decision recognized the fact that significant portions of consumer and healthcare products used in the US are developed and manufactured overseas.

As part of a risk-based approach, the EMA and FDA have developed common procedures for good clinical practice (GCP) and good manufacturing practice (GMP) inspections, and the agencies specifically collaborate in this area to streamline the inspection decision-making process. In the EU, it is common practice for national inspectorates to cooperate with each other and to share inspectors' findings. For centrally authorized products, certain infringements may result in an investigation by the EMA and financial penalties that are levied by the commission under the Penalties Regulation⁷.

As regards GCP, enhanced international cooperation has been recognized by US, Japan and EU regulatory authorities as key to developing a robust harmonized framework for the conduct of clinical trials as more studies are performed in other regions around the world.

In 2015, following an inspection of GVK Biosciences' site in India by the French medicines and healthcare products agency, ANSM, concerns were expressed about how this CRO conducted studies for various pharmaceutical companies that relied on the results to support their product approvals in the EU^{8,9}. The inspection identified data manipulations of electrocardiograms, which appeared to have taken place over a period of at least five years. The systematic nature of the suspected violation, the extended period of time over which it occurred and the number of members of staff involved cast considerable doubt over the integrity of trials conducted at the site generally, and on the reliability of the data generated.

Following its assessment, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended suspension of around 700 pharmaceutical forms and strengths studied at the GVK trial site. Some 300 other pharmaceutical forms remain on the market following the receipt of sufficiently reassuring supporting data from other sources.

Pharmacovigilance

In recent years, and in particular since the introduction of the EU pharmacovigilance legislation in 2012^{10,11}, authorities have been examining more closely the systems that companies use to monitor the safety of their drugs globally. There has been greater scrutiny of how fast and efficient companies are in updating product information and other product related materials on the conditions of use where changes to the product label are agreed in light of new information that has a significant bearing on how to use their products safely and effectively.

In 2011, following the EU referral (i.e., an Article 31 referral) of tolperisone-containing medicinal products, the CHMP made a recommendation to delete certain clinical indications from the product's national marketing authorizations because of adverse reports on hypersen-

sitivity that rendered the product's benefit-risk balance negative. The recommendation resulted in the commission issuing a binding decision obliging the EU member states to take such regulatory measure. A manufacturer then pursued a legal challenge before the European General Court¹² and mounted an appeal in the Court of Justice of the EU¹³ questioning the legality of the commission's decision. The European courts dismissed the applicant's case and ruled that it was sufficient for the commission to point to serious doubts regarding the benefit-risk balance of the product to justify a regulatory measure against a marketing authorization.

As a matter of public policy, given the relevance of pharmacovigilance to patient safety and public health protection, the clear impression created by the authorities' activities is that they are more prepared to take enforcement action to set an example for others. There is currently only one reported case under the EU Penalties Regulation relating to the conduct of pharmacovigilance. This case, which involves Roche litigation in the UK, is concerned with the late/non-reporting of safety information by a US subsidiary of the company, and the infringement has been referred to the commission¹⁴.

The case centred on a re-inspection conducted by the UK Medicines and Healthcare products Regulatory Agency (MHRA) to confirm earlier findings of alleged non-compliance with certain pharmacovigilance obligations. It was alleged that a large number of reports of suspected adverse reactions related to non-interventional programs run by the US affiliate had not been passed to Roche for reporting purposes.

As a result, in October 2012, the EMA notified Roche that it was initiating an infringement procedure under the Penalties Regulation. Thereafter, the MHRA collaborated with the EMA in relation to that procedure whilst also planning a re-inspection. The MHRA sent its final re-inspection report and responses to requests made under the Penalties Regulation to the EMA early in 2014. The EMA has concluded its inquiry and has submitted its report to the commission, Roche and the member states for their consideration. The commission has not yet announced its decision under the Penalties Regulation. However, there have in the meantime been legal proceedings in the UK High Court and Court of Appeal

concerning the MHRA's ability to share information with the EMA on inspections, and the UK courts have ruled in favor of the MHRA.

The main implication of this case is that a marketing authorization holder must assume that any material it provides to the national competent authorities will likely be passed on to the EMA and used in possible infringement procedures under the prevailing regulatory coordination framework. There is also the risk that such material will also be passed on to other competent authorities around the world if there is a relevant link to that jurisdiction.

Manufacturing And Distribution

Global trade expansions also increase the vigilance by regulatory authorities over manufacturing facilities. One of the most significant changes has been in the area of quality assurance applied to ensure data integrity and product quality. A recent increase in the number of incidents where a company's data were falsified or poorly documented has led to new rules being promulgated by authorities, including the UK and the World Health Organization¹⁵, to enhance regulatory oversight. The commission is also preparing revisions to a number of the annexes to the EU GMP guideline¹⁶. The underlying principles set out in these annexes are aligned with the international standards and policies with a view to adopting a harmonized approach to GMP inspections at an international level.

In relation to distribution, the EU legislation on falsified medicinal products, introduced in June 2011, increases the complexity of regulatory requirements and extends the approval system to, and liabilities and obligations on, more entities in the supply chain¹⁷. This has been coupled with a change in the interpretation of the definition of wholesale dealing where a company does not have physical control of the product but is only involved in the sale or the financial part of the supply. There is, therefore, considerable uncertainty as to how these new requirements apply to complex supply arrangements, for example, where products are bought and sold by different entities to those responsible for the physical transportation and storage of the products, and in particular where such transactions involve ex-EU entities.

Advertising Activities

The increased scrutiny of pharmaceutical industry activities, together with greater cross-border collaboration between regulators, have had an immediate impact

on the industry's marketing and advertising activities worldwide. Despite the fact that enforcement activities regarding advertising in most jurisdictions are not as aggressive as in the US, multinational companies are slowly but progressively adopting global compliance benchmarks for all their advertising activities and their interactions with healthcare professionals, payers and other stakeholders.

Enforcement in this area continues to focus on off-label claims, promotion on the Internet and via mobile applications, and interactions between companies and healthcare professionals or payers that involve a financial element. Moreover, there is a growing emphasis on transparency in engagements between industry and healthcare professionals, including financial arrangements.

There is also more scrutiny over non-promotional medical activities such as market research, post-marketing research and advisory boards, which has increased the need for companies to clarify their medical and commercial boundaries and to revise carefully their contracting procedures to separate research contracts from promotional activities. In some European jurisdictions such as Germany and the UK, the regulatory authorities and the self-regulatory bodies controlling pharmaceutical advertising have been increasingly analyzing the interactions between medical and commercial roles of company representatives, and the organizational structure of the companies.

Conclusion

The growing complexity of the global business environment over the past 15 years has resulted in greater compliance monitoring by the regulators and more enforcement actions.

The public also demands greater transparency in regulatory decision-making and corporate accountability, the latter of which has resulted in companies becoming increasingly interested in addressing compliance risks in the areas of strategy and business transformation. The evolving healthcare delivery landscape and the increasing use of third-party contractors also continue to challenge compliance oversight.

These market changes come at a time when ensuring confidence in the sector is critically important. The industry constantly prioritizes risk in a manner that aligns with the evolving regulatory landscape and the

attitude of the regulatory and enforcement authorities. Companies generally recognize that a good governance and compliance structure reflects their growing awareness and acceptance of social responsibility. They are also aware that there are costs and reputational risks at stake from non-compliance, in addition to business disruption.

Regulatory compliance models of the future will need to strike the right balance between being responsive to compliance risks and being proactive by managing and mitigating such risks in real time.

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