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MINI-ROUNDTABLE

COMPLIANCE AND ENFORCEMENT OF FDA-REGULATED PRODUCTS

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Christopher M. Mikson is a partner in Washington DC, where he serves as leader of Mayer Brown's Food and Drug Administration (FDA) regulatory practice and co-leader of the firm's healthcare practice. With his unique combination of training and experience as a physician, registered patent attorney and trial lawyer, he focuses his practice on FDA regulatory matters and complex litigation and transactional matters involving healthcare and the life sciences. LMG Life Sciences recognised him as a 'Life Sciences Star' in 2018 and 2019.

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Sonali P. Gunawardhana is of counsel in the Washington DC Office of Shook, Hardy and Bacon LLP. Gunawardhana draws on nearly 10 years of experience as an attorney at the FDA to offer clients detailed and practical guidance on how to avoid and resolve FDA regulatory challenges. She gives her clients the benefit of her deep knowledge of the law and a keen, forward-looking sense of how the FDA may view a particular matter, allowing the client to develop the most effective and persuasive approach to any situation. LMG Life Sciences recognised her as a 'Life Sciences Star' in 2015, 2016, 2017 and 2018.

CD: Across the product lifecycle – from clinical trials and the pre-market review process through to post-market compliance – what general steps does a US Food & Drug Administration (FDA) compliance strategy need to include?

Mikson: The precise issues and steps to be taken regarding Food and Drug Administration (FDA) regulatory compliance vary at each of the different stages of the product lifecycle. However, there are general strategies and priorities that are common to most, if not all stages of the product lifecycle. At the outset, the sponsor must have a clear and thorough understanding of FDA regulations, guidance and practices in the therapeutic area at issue that will be applicable at each point in the process. For example, drugs in the oncology area may have particular clinical trial standards applicable because of the nature of the disease and patient populations, which may include an enhanced ability to utilise adaptive clinical trial design and possibly real-world evidence. As the process moves forward, the sponsor needs to be prepared to engage the FDA 'early and often', and to be proactive in taking advantage of informational meetings and more substantive meetings that are available throughout the ongoing development, testing and approval processes. Finally, at a high level the sponsor should take care to assess and implement a plan for coordinating the FDA strategy with other critical areas such as intellectual property (IP) and reimbursement. To that end, parties must ensure that the FDA's lawyers and consultants, the patent lawyers and the reimbursement experts are all talking to each other and are working together from the very beginning of the product lifecycle.

Gunawardhana: A compliance strategy is highly dependent on understanding the regulations that apply to your product from inception throughout the product lifecycle. The FDA continues to provide guidance documents on a variety of regulatory issues so that regulated industry can understand how best to comply with the various governing regulations. Also, the FDA will meet with industry at various stages of the product lifecycle in order to assist in maintaining compliance from pre-market approval through to post-approval marketing. It is best to hire those who have the requisite education and experience to assist with every stage of the product lifecycle and to adopt a corporate culture of compliance. Having knowledgeable employees in all departments of the company will assist in recognising when corrective action should be implemented, in accordance with company culture and allowing for a successful compliance strategy.

CD: How would you characterise the FDA's monitoring and enforcement efforts in recent years?

Gunawardhana: The FDA continues to monitor enforcement efforts, though the number of regulated products continues to grow. In recent years, there has been an overall downward trend in the number of enforcement letters issued by the FDA but this is not necessarily a true indicator of the FDA's enforcement efforts given that the FDA has other enforcement options at its discretion that are not necessarily publicised, such as requesting regulatory meetings. The FDA also partners with other agencies, such as the Federal Trade Commission (FTC) and the Department of Justice (DOJ), in order to take meaningful and appropriate enforcement actions to protect the nation's public health.

Mikson: It has been reported that statistically the FDA's enforcement efforts have declined under the current administration. In July 2019, Science reported that the number of warning letters issued in the drug and device spaces had fallen by a third, warning letters from the Center for Drug Evaluation and Research's (CDER's) district offices in Philadelphia, Florida and New York had fallen by more than two-thirds and that two district offices have not issued any warning letters in more than two years. One area that seems to have increased is where there are inquiries or warnings from the agency based on the FDA's monitoring of the internet in general, and social media in particular.

CD: Should an adverse event occur, and a warning letter issued, how should a company respond in the first instance?

Mikson: Companies should always be prompt, proactive, accurate, precise, truthful and transparent in their responses and communications to the FDA, as well as to other agencies and in press releases, where there is an adverse event or unfavourable development with respect to their FDA-regulated product. A corollary to that approach is that the company should strive to foster a relationship of trust and respect with the FDA, starting with their very first interaction with the agency. We have found that the latter often pays dividends when the former arises. In any event, once such a situation arises, we have found that the agency appreciates candour and responds much more favourably to open and honest communication rather than any attempt to challenge unfairly, circumvent or rely on a strained interpretation of the regulations or guidance. To be sure, there are times when it is advisable to challenge the agency. However, in those instances the likelihood of success and the risk and benefits of taking an adversarial approach with the agency should be carefully considered.

Gunawardhana: As adverse events are reported, companies are required to take certain actions, such as reporting the adverse event to the FDA and

undertaking an internal investigation to identify the root cause of the problem reported, generally all well before a Warning Letter is issued by the FDA. The company should do everything it can to address and correct any defect it may uncover. This may result in taking wide-ranging corrective action, such as issuing a recall of the product and a press release with all the pertinent information to address the consumer's questions. Should a warning letter be issued to the company, it is imperative that the company respond with a comprehensive written response within 15 business days, however remediation should start the day after receiving the regulatory correspondence.

CD: Going forward, what information typically needs to be included in a corrective action and preventive action (CAPA) plan, in order to restore FDA-compliance status?

Gunawardhana: Depending on the issues discovered, the company should conduct a thorough root cause analysis and one or more corrective and preventive actions (CAPAs). With every CAPA initiated there should be a time frame in which the investigation is conducted and corrective actions are fully implemented. It is important to ensure that executive management, key functional heads, regulatory and quality, legal and compliance are aware of what corrective and preventative actions are taking place. CAPAs often require additional training of personnel, thus it is imperative that appropriate staff receive training and that the training is comprehensive and well-documented. In other instances, the CAPA requires parties to review the quality agreement with suppliers; in these situations it is important that companies see if the changes require additional remedial actions, such as issuance of a field correction or recall.

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> *Christopher M. Mikson, Mayer Brown LLP*

Mikson: The most important thing is to capture every question and issue raised by the FDA in the applicable agency communication, and ensure that each such matter is clearly identified, plainly and thoroughly addressed, made the subject of a mechanism to remediate and assess it on an

ongoing basis, and that a follow-up reporting plan and schedule be put in place and strictly followed. It is often prudent and advisable to avoid raising expectations any farther than what is realistic to accomplish, and with a safety margin if feasible, both in terms of substance and timing. The worst thing you can do is to tell the FDA you will have a problem completely resolved in 30 days and you will report within that time frame, but then fail to accomplish either or both promised actions. It is usually much better to inform the FDA of what is happening, say why it will take as much time as it will, explain why a more aggressive approach would be unrealistic and counterproductive, and faithfully provide regular interim reports on progress toward the stated realistic goal.

CD: To reduce the potential for non-compliance, what advice would you offer companies in terms of product development, including safety, labelling and promotional considerations?

Mikson: Generally speaking, there are two types of regulatory approaches by the agency applicable to FDA-regulated products: those that require premarket authorisation, such as drugs, biologics and non-exempt medical devices and those that are subject to FDA scrutiny after they enter the market, such as food and cosmetics. With respect to the former, it is critical that the company has full information and a complete understanding of the regulatory basis on which the agency based its findings of safety and effectiveness. For example, the more a product has a narrow therapeutic index, the more any modifications to any aspect of the product, including ingredients or components and methods of manufacture, will likely trigger FDA activity, whether that be enforcement or a requirement for a new regulatory submission. With respect to the latter, there is typically more room for interpretation and gradation of risk, since there may not be a pronouncement from the agency that is exactly on point, and there is also the possibility that the agency might not consider the issue a high-enough risk or priority to pursue enforcement action.

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Gunawardhana: The area where there is a real potential for non-compliance is promotional considerations. When a company works closely with the FDA during product development in terms of the safety profile and approved labelling of the product, there is solid guidance on how those two areas are to be managed. Promotional labelling must be done with many considerations in mind, such as platform and audience. It can be difficult to navigate how best to present information about a product when balancing information regarding both the risks and benefits. Many companies find themselves traversing a fine line, especially when working with social media platforms. In order to ensure that all promotional materials are appropriate, it is best to have representatives from the legal, medical and regulatory departments review them prior to dissemination.

CD: Drilling down, what advice would you offer to companies on anticipating and mitigating FDA-related risk during a product marketing campaign?

Gunawardhana: The FDA issues a fair amount of regulatory correspondence in the form of warning letters. These letters are good indicators of the regulatory boundaries that should be followed in terms of promotional material. In fact, the FDA hopes that these letters will be used as signposts by regulated industry so that they can both self-monitor and police their own actions. The FDA has issued numerous guidance documents regarding promotion and advertising on a variety of platforms. These documents provide the FDA's best thinking on a matter and provide both best practice, as well as regulatory references in order to understand how best to operate in a compliant manner.

Mikson: All marketing and promotional statements and materials must be truthful and non-misleading, and they are judged not only on their express language but also on what their language and any additional content, such as images, might reasonably imply. For that reason, we tend to suggest to parties that more than one person review the subject material, including lawyers as well as business and marketing professionals. Where a product is subject to FDA premarket authorisation, the line for permissible content tends to be well demarcated, that is to say the marketing and promotional statements must not be expanded beyond the scope of the approved indications and the approved labelling. In addition, there is a mechanism for a sponsor to voluntarily request prior review by the FDA of promotional materials and statements. While some off-label promotion is permissible under recent case law and agency policies, that line remains somewhat unclear. Accordingly, we tend to think it is prudent to be conservative and err on the side of caution in such situations. Where a product is not subject to FDA

premarket authorisation, the line may be somewhat less clear, and thus there may be some room for interpretation. In that case, the balancing of risk versus benefit of certain promotional statements may be a matter of judgment, even a bit subjective, rather than that of not crossing a clearly demarcated line. Ultimately, we usually find that by having the lawyers and the marketing and business experts working closely together as a team, potential problems can be mitigated or avoided by making relatively minor alterations to content without detracting significantly from the desired promotional message.

CD: What are your predictions for FDA regulatory scrutiny and enforcement action in the years ahead? How might a new US administration impact the FDA's power to enforce its requirements?

Mikson: Since the FDA is part of the US Department of Health & Human Services (HHS) and an arm of the executive branch, the policy of the administration may directly and significantly control the level of regulatory scrutiny and enforcement action undertaken by the FDA. Having said that, FDA commissioners can exercise a significant level of their own discretion in interpreting applicable statutory authority, promulgating regulations and applying those regulations by issuing guidance and making regulatory and enforcement priorities and decisions. The recent tenure of Dr Scott Gottlieb is an interesting study of this concept. Coming in, many inside and outside the agency believed Dr Gottlieb would be essentially an arm of the administration and the drug industry, and as such he would reduce regulatory scrutiny by the agency to a large degree. However, in the actual event Dr Gottlieb proved to be a relatively independent commissioner, highly proactive and even aggressive in pursuing his own agenda as to issues he considered a priority. This tact ironically paralleled the approach of the president, at least superficially, insofar as the reliance on social media is concerned. As of this time, we are awaiting the confirmation hearing for Dr Stephen Hahn to be held before the Senate Health, Education, Labor and Pensions (HELP) Committee on 20 November 2019. Given Dr Hahn's private-sector background there is little or no government track record for him, and so as matters now stand it is difficult to predict how his leadership would affect FDA regulatory scrutiny and enforcement activity. One thing we can say is that if Dr Hahn becomes commissioner, much of this determination will come directly from him, meaning there are questions regarding whether and to what extent he closely follows the policies of the president or seeks to blaze his own path. Stay tuned.

Gunawardhana: The FDA tends to be consistent in its approach when it comes to enforcement actions, regardless of a new administration, but the priorities may shift based on the new

administration's goals. As many of the enforcement activities span over the lifecycle of products, the agency tends to be consistent in its approach. As we are dealing with a global economy, we believe that the FDA will look to further partner with other international regulatory authorities in order to protect the nation's public health. In addition, we believe that the FDA will continue to take enforcement action against various types of cannabidiol and vaping products that put teens and vulnerable people at risk. CD