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World of Change Coming For Device Manufacturers: Developments In FDA And International Inspections

By Nathan A. Brown and Howard R. Sklamberg

DEVICE COMPANIES HAVE AN OPPORTUNITY TO leverage several major reforms and initiatives that are getting off the ground related to global facility inspections. But firms must constructively engage with the new programs to reap benefits, say Akin Gump attorneys and former top US FDA officials Nathan Brown and Howard Sklamberg in this guest column.

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As medical technologies have become increasingly sophisticated and varied, US FDA has been confronted with the need for a more specialized inspectorate. Similarly, the increasingly globalized nature of medical device production has stretched FDA's inspection resources, leading the agency to explore ways of working collaboratively with other regulators around the world. In turn, device-makers have had to grapple with FDA's changing expectations, the potential for varying standards imposed by different regulators across the globe, and a lack of clarity as to FDA's specific expectations for addressing inspection observations.

FDA and Congress have recently taken significant steps to improve regulatory efficiency and predictability in the inspection of medical device facilities. Device-makers will need to adjust their practices to take advantage of three important initiatives that have advanced in recent months:

- FDA has implemented the Program Alignment initiative to increase the specialization of investigators and their supervisors.
- Congress enacted the FDA Reauthorization Act of 2017 (FDARA), which reforms FDA's inspections practices for medical device establishments.
- FDA and other regulators have made significant progress toward implementing the Medical Device Single Audit Program (MDSAP), which allows multiple countries' regulators to rely on a single inspection.

These changes, if implemented effectively, offer device-makers opportunities to streamline and enhance their compliance and quality programs.

Program Alignment

On May 15, FDA implemented Program Alignment in its Office of Regulatory Affairs (ORA), which, among other functions, conducts inspections of medical device manufacturers. *(Also see "'Program Alignment' Falls Into Place: Everything You Need To Know About US FDA's New Inspectional Approach" - Medtech Insight, 8 May, 2017.)*

Program Alignment is a reorganization of the 5,000-person ORA that shifts management of operations, including inspections, from one that is based on geography to

one based on areas of regulatory expertise. Investigators and their supervisors will be now be housed in one of seven offices: Medical Devices and Radiological Health; Biologics; Import Operations; Pharmaceuticals; Bioresearch Monitoring, which oversees clinical trials; Human and Animal Food; and Tobacco. Prior to Program Alignment, ORA assigned investigators to geographic regions, and investigators would generally oversee FDA-regulated facilities within that region, regardless of product type.

Device establishments should view Program Alignment as an opportunity to develop a more cooperative relationship with investigators who will be increasingly dedicated to understanding their particular technologies.

Although most FDA investigators were already specialized by commodity type, Program Alignment will ensure that *all* FDA investigators are specialized, making it easier for investigators to remain up to date on medical device technology and policy while not having also to focus on, say, food safety policy. It will also ensure that the supervisors who help decide which facilities to inspect and review recommendations for compliance actions are medical-device specialists. Prior to Program Alignment, these supervisors had responsibility for all commodities in their geographic area, regardless of their own expertise. Because investigators and supervisors are now responsible for only one commodity, they will have the opportunity to work more closely with FDA's Center for Devices and Radiological Health.

A closer working relationship between specialized ORA supervisors and investigators and CDRH experts should improve predictability and consistency. It remains to be seen how ORA will implement the device-focused investigators across a wide array of device technologies: Will there be subspecialists focused on diagnostics, for example, or on software-only medical devices?

ABOUT THE AUTHORS

Nathan A. Brown (left) is a partner in Akin Gump's health care and life sciences practice who focuses on food and drug law. He formerly served as an FDA detailee as health policy advisor to the Senate Health, Education, Labor and Pensions (HELP) Committee and as special assistant to the FDA chief counsel.

Howard R. Sklamberg (right) is also a partner in the firm's health care and life sciences practice focusing on food and drug law. From January 2014 to April 2017, he was the deputy commissioner for global regulatory operations and policy at FDA.

For the moment, when responding to inspections or engaging with FDA, it is important for firms to understand the roles that the relevant officials will play in the newly reorganized ORA, and to anticipate some transition in the investigators and supervisors with whom they typically engage. Over the longer term, device establishments should view Program Alignment as an opportunity to develop a more cooperative relationship with investigators who will be increasingly dedicated to understanding their particular technologies.

FDA Reauthorization Act

On August 18, President Trump signed FDARA, which reauthorizes user fees for pharmaceuticals and medical devices for five years. *(Also see "MDUFA IV (And More) Is Law: Trump Signs A Health-Care Bill" - Medtech Insight, 18 Aug, 2017.)* FDARA contains provisions that touch many aspects of device regulation. One key focus of FDARA's device provisions is improving efficiency and

predictability with respect to inspections and resulting inspection observations (known as "483s," after the form on which they are conveyed).

For device establishments, the FDARA reforms may dictate corresponding revisions to their internal procedures governing the conduct of inspections and responses to inspection observations.

Under FDARA, FDA must implement a risk-based medical device inspection schedule. The inspection schedule will be arranged based on factors such as the nature of the device, compliance history, its past inspection frequency, and whether the establishment participates in an international audit program (such as MDSAP). Making inspections formally risk-based will reduce the resource drain from inspections that have limited public health utility. FDARA's nod to international audit programs and discouraging duplicative inspections acknowledges the resource challenges associated with globalization.

FDARA also requires FDA to improve the transparency and predictability of inspections, expand opportunities for communications, and facilitate the resolution of inspection observations. The process improvements are designed to address an industry concern that FDA's inspections decisions are sometimes unpredictable and opaque. In particular, FDARA directs FDA to announce device inspections in advance, with estimates of the timeframe for the inspection and an opportunity for advance communications with the inspection team concerning topics such as the establishment's typical hours of operation and the types of records to be reviewed. In addition, FDA is directed to develop policies providing for inspections to take place on consecutive days (rather than sporadically over a period of time) and to develop standardized communications templates to facilitate more consistent information exchange. FDARA establishes deadlines for FDA to publish draft and final guidances that implement these changes.

Even more significantly, FDARA creates an opportunity for device establishments to request informal feedback on their proposed corrective actions to address certain deficiencies identified during an inspection. This provision addresses concerns by device sponsors that they often undertake costly or complex corrective actions without any clear signal from FDA that their actions will fully address the agency's concerns. Under FDARA, if an FDA inspections report contains observations and related corrective actions that implicate a public health priority or an emerging safety issue, or would involve systemic or major undertakings by the establishment, then FDA must respond to a request for "non-binding" feedback on the proposed actions within 45 days.

These changes create a new paradigm for device inspections, which, if implemented constructively, will complement and enhance FDA's Program Alignment initiative. For device establishments, these changes may dictate corresponding revisions to their internal procedures governing the conduct of inspections and responses to inspection observations. To take advantage of these changes, device establishments should work proactively to leverage these enhanced opportunities for open communication with FDA before, during, and after an inspection. More importantly, by providing for advance communications about corrective actions between the establishment and FDA personnel—rather than FDA only assessing changes retroactively—FDARA has improved the likelihood that establishments will be able to satisfy FDA's expectations as quickly as possible.

Medical Device Single Audit Program

The medical device market has become increasingly global. FDA estimates that imported medical devices constitute 35 percent of the US market. FDA and other regulators must increasingly conduct oversight of products manufactured or developed outside their borders. The need to conduct foreign inspections creates a resource challenge for FDA because foreign inspections incur additional travel and planning costs. Also, if foreign regulators do not coordinate their activities, a firm may be inspected repeatedly, in a short time span, by different regulators, with inconsistent results. Con-

versely, other firms might be inspected too infrequently, due to lack of resources—potentially leaving safety risks unidentified.

On June 29, the MDSAP Regulatory Authority Council issued a report concluding that a pilot of MDSAP was successful, signaling that the program will continue.

MDSAP is designed to address these challenges. *(Also see "More Manufacturers Sign Up For Single Audits As MDSAP Becomes Operational" - Medtech Insight, 16 Feb, 2017.)* MDSAP allows a "recognized Auditing Organization" (an entity authorized to audit under MDSAP requirements) to conduct a single, standardized regulatory audit of a medical device manufacturer. The five countries that currently participate in MDSAP (Australia, Brazil, Canada, the US, and Japan) then rely on this audit. The European Union is an Official Observer to the MDSAP's governing board, the Regulatory Authority Council, and may choose to join MDSAP in the future. Each of the five MDSAP regulators uses the audits slightly differently. FDA will accept an MDSAP audit report as a substitute for many FDA routine inspections, but not as a substitute for "for cause" or "compliance follow-up" inspections. Notably, under the FDARA reforms, MDSAP participation will also result in lowering an establishment's risk profile. On June 29, the MDSAP Regulatory Authority Council issued a report concluding that a pilot of MDSAP was successful, signaling that the program will continue.

MDSAP participants will be audited on a three-year certification cycle, with one audit occurring each year. The first-year audit, called an Initial Certification Audit, is a complete audit of a medical device manufacturer's quality management system (QMS). This audit determines if MDSAP documentation and regulatory requirements have been met, and evaluates technology used by a manufacturer. The Initial Certification Audit is followed by two yearly partial Surveillance Audits conducted once per year for two years. The cycle then recommences with a Recertification Audit. Other audits by regulatory agencies, including "for cause" inspections, may still occur.

The MDSAP audit process has several advantages, for firms and FDA. MDSAP allows the regulatory assessment process among multiple governments to be serviced by one auditor, meaning there is less business disruption and more consistency. MDSAP audits are announced, scheduled by the Auditing Organization with the manufacturer, and assigned a pre-established duration, minimizing business disruptions to the device company.

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