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## Enforcement

# Reforming the 483: FDA's Modernization of Its Process for Documenting Inspection Results



BY HOWARD R. SKLAMBERG

In a recent speech to the National Association of State Departments of Agriculture, Food and Drug Administration Commissioner Scott Gottlieb stated that he had “heard the concerns you’ve raised regarding the use of the traditional FDA 483 to document regulatory issues during produce inspections, and you have asked for us to consider additional approaches.” He went on to indicate that he has instructed FDA staff “to explore additional ways of communicating our concerns about what we observe during produce inspections” (see Scott Gottlieb’s Sept. 12 speech to the 2017 NASDA Annual Meeting).

There are two sets of problems with “the traditional FDA 483,” which is the form that FDA investigators have used for decades to document potential violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

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*The views expressed in this piece are solely those of the author.*

These problems and the need for reform affect not just produce, but all of the commodities FDA regulates.

The first area of concern involves agency procedures. Investigators generally have broad discretion on whether to issue a 483 and what violations to cite. The process for a firm to request and obtain corrections to a 483 is unstructured and rarely used, which is consistent with FDA’s belief that a 483 is a preliminary document that is part of a lengthy agency review process. Over time, the world outside of FDA has taken a different view – 483s now have profound effects on inspected firms and other stakeholders. FDA’s current corrections process is inconsistent with this reality.

The second area of concern is more substantive. The 483 is an unstructured document that is used for practically all of FDA’s inspections, from produce and manufactured food to high risk medical products and clinical trials. FDA is in the process of implementing new laws and regulations and rethinking many aspects of the ways it inspects across all commodities. As inspecting has become more specialized, in its Program Alignment initiative, FDA has reorganized itself, making its investigators and supervisors specialists in one commodity. The forms and procedures that FDA uses should also be specialized and reflect its evolving approach to inspections.

FDA’s process for issuing 483s is straightforward. At the end of an inspection, an investigator in FDA’s Office of Regulatory Affairs (ORA) issues a 483 when he or she observes “any conditions that in [his or her] judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts” (FDA Form 483 Frequently Asked Questions). This step complies with the requirement of Section 704(b) of the FDCA that “[u]pon completion” of an inspection, the investigator “shall give” to the firm “a report in writing setting forth any conditions or practices observed by him which, in his judgment” indicate that a regulated product is contaminated or “prepared, packed, or held under insanitary conditions. . .” Investigators discuss potential 483 observations with the firm during the inspection and at the inspection close-out. The issuance of the 483 begins a lengthy agency review process in which: firms may

submit written comments; the investigator prepares an Establishment Inspection Report (EIR) that evaluates the 483, material collected during the inspection, and the firm's 483 response; and supervisors in ORA and the relevant FDA product Center review the EIR and classify the inspection as No Action Indicated, Voluntary Action Indicated, or Official Action Indicated and decide whether a compliance action is necessary. The EIR is a much more comprehensive document than a 483 and is written under less time pressure than an investigator faces when writing a 483. FDA's final classification decision is the product of a thorough agency review. With the benefit of time and a consultative process, ORA and Center experts may take a different view of a 483 observation from an investigator who had to prepare a report before ending an inspection. Thus, the EIR and final classification may differ from the impression left by a 483. These variations are no more surprising than decisions by an appeals court to alter an on-the-spot decision made by a judge during a trial.

The variation between a 483 and the agency's final assessment of an inspection can be critical for a company or clinical investigator. As soon as FDA issues a 483, it is subject to release under the Freedom of Information Act. Indeed, FDA proactively posts 483s that it believes are of public interest, and in some instances, have begun doing so routinely. Many websites compile 483s and create searchable databases. The release of a 483 can significantly affect a firm's or clinical investigator's standing among patients, consumers, the medical community, retailers, investors, and other stakeholders. Retailers, for example, may choose one product over another because a firm has received a 483 or because one firm's 483 contains more observations than another's. The press actively reports on 483s, and firms sometimes make personnel changes because they receive an adverse 483. At conferences, presenters summarize the most frequent annual 483 observations as indicating current agency thinking. Despite the agency's efforts to treat 483s as not legally binding, they can become significant in litigation and in foreign and state regulatory proceedings.

Sometimes, 483 observations are clearly significant and the immediate effect on a firm is well justified. But when FDA later concludes that 483 observations were less significant than they had seemed or even incorrect, it is difficult to reverse the perception left by the 483. FDA often takes months to complete the EIR and make its final classification decision, leaving the 483 as the only public record related to the inspection. After the EIR is completed and the inspection is classified, FDA generally does not revisit the applicable 483.

Given the consequences of receiving a 483, the need for an effective process to correct 483s is important. Section 5.2.3.1.6 of FDA's Investigations Operations Manual emphasizes that 483s are "of critical importance to both the Agency and regulated industry" and that "complete and accurate documentation of corrections to this official document is critical." It provides that investigators may correct 483s before or after leaving an establishment and should "[d]iscuss any errors with [their] supervisor." It does not discuss how a firm should initiate a request for correction or what procedure FDA should follow other than the investigator/supervisor consultation. It does not indicate whether FDA's Centers should provide input or who is the final decisionmaker. It does not specify what standard FDA

should employ in reviewing an objection to a 483. As FDA's Regulatory Procedures Manual shows, this lack of specificity is quite different from FDA's approach to documenting procedures for compliance and enforcement actions.

Aside from the correction process, industry should engage with FDA to change the substance of 483s. To better serve its public health mission, FDA is modifying its approach to inspections across the commodities it regulates. The current 483 is a form that does not differentiate among types of inspections or emphasize FDA's public health priorities for inspections.

The change in FDA's approach to food safety is a good example. Prior to the passage of the FDA Food Safety Modernization Act (FSMA), investigators' primary responsibility was to record violations, which could lead to enforcement actions, which would incentivize compliance through deterrence. FSMA shifted FDA's focus to prevention – firms must now develop and implement more comprehensive plans to prevent risks to food safety. With this shift, FDA has adopted an approach of "educate before and while we regulate" (see May 22 post on the FDA's blog, *FDA Voice*). FDA continues to take enforcement action to protect public health, but investigators look not just for potential violations but also educate firms and note efforts to achieve compliance. A 483 for food inspections might require investigators not just to list violations but to record observations consistent with this broader approach. Under FSMA, different sets of rules apply to produce versus manufactured food. Some foods, such as seafood and juice, are covered by Hazard Analysis and Critical Control Point rules that differ from FSMA requirements. Dietary supplements are exempt from many FSMA requirements and subject to their own set of Current Good Manufacturing Practices. Industry should press for new 483s that vary and reflect FDA's public health priorities.

FDA's approach to medical product inspections is also changing rapidly. In pharmaceuticals, FDA has recognized the need for reform by launching a New Inspection Protocol Project (NIPP), which "is expected to provide a more quality-focused, semi-quantitative approach with streamlined and structured inspection reports" that will "increase the quality focus of investigator assessments, so that facilities and behaviors found to exceed basic compliance can be recognized as such" (see "FDA Pharmaceutical Quality Oversight: One Quality Voice"). The NIPP project recognizes that a 483 that only documents violations is inconsistent with this broad public health goal. Under the Case for Quality (CfQ) initiative, FDA is shifting its focus in medical device oversight to "critical-to-quality practices that result in higher quality outcomes." In a CfQ pilot, FDA considered the need to prioritize 483 observations to better reflect the agency's critical-to-quality focus. Early this year, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, of which FDA is a leading member, proposed renovations to the E6 Guideline for Good Clinical Practice (GCP), which outlines standards for clinical trials. Former Commissioner Robert Califf has called for a fundamental rethink of clinical trial oversight. If FDA were to reevaluate its GCP rules or priorities, that could also affect how inspections are conducted and how investigators would document their findings.

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Stakeholders should engage with FDA as the agency implements Commissioner Gottlieb's directive to consider new approaches to documenting investigators' observations. They should press for a process that is con-

sistent with the powerful effect of inspection reports and with FDA's efforts to promote public health by modernizing its approach to inspections.