# A Client's Guide to FDA Inspections

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*A Food and Drug Administration (FDA) inspector has just knocked on your door and announced that he or she will now inspect your facility. What happens before, during and after this inspection, and what should your firm do to prepare for each stage?*

*Here are answers to a number of frequently asked questions about FDA inspections and compliance actions. These answers are designed to be generally applicable, rather than addressing a specific type of product. In future client guides, we will discuss some specific items for food, drugs and medical devices, and some likely changes that FDA will make pursuant to new laws, such as the FDA Reauthorization Act of 2017 and the FDA Food Safety Modernization Act (FSMA).*

### *Q. Who conducts FDA inspections?*

***A.*** Almost all FDA inspections are conducted by Consumer Safety Officers in the Office of Regulatory Affairs (ORA). Consumer Safety Officers, colloquially called investigators, are trained to conduct inspections for a specific FDA-regulated commodity. They report to ORA supervisors within the same specialty—for example, drug specialists oversee drug investigators. Investigators in the Office of International Programs (OIP) perform some inspections in locations in which FDA has a foreign office. These OIP investigators are usually on temporary assignment from the ORA, are specialized and have received the same training as those in ORA. Occasionally, experts from the relevant FDA product center accompany ORA investigators. FDA's Office of Criminal Investigation does not participate in regulatory inspections.

### *Q. Will FDA's Program Alignment initiative change who inspects my facility?*

***A.*** On May 15, 2017, FDA implemented its Program Alignment initiative, which is a reorganization of ORA that shifts management of inspections and compliance from a geographic structure to one based on commodity. Before Program Alignment, although most investigators were specialized by commodity, some performed inspections of facilities in their geographic area, regardless of commodity type. Also prior to Program Alignment, an investigator could report to a specialist in a different commodity because the two worked in the same geographic district. Now, all investigators and supervisors will be specialists in the facilities that they oversee.

If a firm has been inspected by nonspecialists, the identity of the investigator in future inspections will likely change. Also, because Program Alignment changes investigators' supervisors, if a firm wishes to dispute an investigator's actions or conclusions, the relevant ORA officials will also change.

### *Q. What types of inspections does FDA conduct?*

***A.*** In FY 2016, FDA conducted more than 16,000 domestic inspections and 3,500 foreign inspections, and contracted with states to perform more than 20,000 inspections.

There are three basic types of inspections of manufacturing facilities. Preapproval inspections are part of the process that FDA uses to evaluate whether to approve some medical products for sale in the United States, such as most prescription drugs and high-risk, "Class III" devices. Because there is no preapproval process for food, preapproval inspections are not part of FDA's food program. "Surveillance inspections" are routine assessments of whether a facility is complying with FDA's rules and regulations. FDA conducts these inspections after a product is on the market. "For-cause inspections" occur in response to a specific trigger, such as a recall, an outbreak, laboratory testing results or information from a whistle-blower. FDA also performs for-cause inspections to verify that a firm has taken corrective actions that rectify a problem that FDA had previously identified. These inspections are also called "follow-up inspections."

FDA conducts inspections of FDA-regulated research pursuant to its Bioresearch Monitoring Program. These inspections cover clinical trials, nonclinical testing laboratories and bioequivalence facilities. FDA also performs inspections of tobacco manufacturing facilities and contracts with states, territories, and third-party entities to inspect tobacco retailers.

### *Q. How does FDA decide where to inspect?*

A. FDA uses risk-based models to determine where to conduct surveillance inspections. The models differ based on commodity, but, generally, inspections are more frequent when the product is riskier (for example, a sterile injectable drug versus an over-the-counter tablet), the site has a poor compliance history, and the site has

not recently been inspected by FDA or other trusted regulators. ORA and the product centers collaborate in choosing where to inspect. FDA considers similar factors when deciding whether to conduct preapproval inspections.

"For-cause" inspections usually occur promptly after a triggering event, particularly if the agency determines that there is a significant public health risk.

Under limited circumstances, FDA may waive a preapproval inspection for approval of some medical products.

In some areas, the law establishes a minimum inspection frequency. For example, FSMA contains a series of food inspection mandates.

***Q. Will my inspection be announced ahead of time?***

***A.*** Not necessarily. Many FDA inspections are unannounced.

***Q. How should a firm prepare for an inspection?***

***A.*** Although most inspections are unannounced, firms often can anticipate that they will be inspected in the near future, depending on the factors described above.

The specifics of preparation depend on the type of inspection. Generally, firms should have procedures in place for responding to FDA inspections—for example, specifying who will be the lead for interacting with the investigator, where the investigator will review documents, and which counsel or technical expert the firm would consult if a problem were to arise.

***Q. What happens during an inspection?***

***A.*** At the beginning of an inspection, the investigator will present his or her credentials and an FDA Form 482, the "Notice of Inspection."

Inspections vary by the type of product and the size and complexity of the facility. For example, in a drug manufacturing facility inspection, FDA will often examine six systems—quality, production, facilities and equipment, laboratory controls, materials, and packaging and labeling. In a food inspection, FDA will determine whether a firm has complied with the appropriate preventive controls described in the regulations implementing FSMA or with the Hazard Analysis Critical Control Point rules that apply to seafood, and juice. In device inspections, FDA focuses largely on compliance with the Quality Systems Regulation. In practically any type of inspection, investigators will examine relevant records and processes, such as the standard operating procedures for recalls, laboratory test results, whether production employees are properly trained and attired and follow procedure, whether a facility is appropriately sterile or clean, and whether a firm monitors its operations and takes appropriate corrective action. Investigators will talk to employees and collect records, will sometimes obtain product samples or environmental samples, and may take photographs. Usually, one or two FDA investigators conduct an inspection; additional investigators might be involved in more complex inspections.

A firm employee or employees should accompany the investigator during the inspection to respond to questions or information requests. It is important for the firm to take notes of the information requested and provided and what has transpired.

At the end of each day, the investigator usually summarizes any problems that he or she detects. The firm should point out any areas in which it disagrees with the investigator as soon as the investigator raises them.

***Q. How does the inspection end?***

***A.*** At the conclusion of the inspection, the investigator will issue a form entitled "Inspectional Observations," known as "FDA Form 483" or simply a "483," when, "in

the investigator's 'judgment', conditions or practices observed, indicate that any food, drug, device, or cosmetic have been adulterated or are being prepared, packed, or held under conditions whereby they may become adulterated or rendered injurious to health."[1] The investigator issues the 483 at a closeout meeting, which concludes the inspection. If the firm disagrees with an item on the 483, it should voice that disagreement at or before the closeout.

Inspections vary considerably in length, depending on the size and complexity of the facility and what the investigator finds. FDA must conduct inspections "at reasonable times and within reasonable limits and in a reasonable manner."[2]

***Q. Are there limits on the types of records that FDA may request during an inspection?***

***A.*** Yes. The types of records that FDA may request is quite broad, but there are limitations, set forth in 21 U.S.C. 374, that vary by commodity. For example, FDA has limited authority to obtain certain financial data, sales data, pricing data, personnel data and research data.

***Q. How should a firm respond to FDA information requests during an inspection?***

***A.*** It is important to provide truthful and complete responses to lawful FDA questions and information requests. FDA inspections are governed by laws that make it a crime to obstruct, or provide false information in, federal proceedings.

If a firm believes that an investigator has overstepped, the firm should seek counsel promptly. If a firm declines to provide information that FDA may lawfully request or causes an unreasonable delay to FDA's ability to obtain information or complete its inspection, FDA could initiate enforcement action.3 It is therefore important that a firm's objection have a strong legal and factual basis.

***Q. If a firm raises a significant objection with an investigator and continues to disagree with the investigator's response, are there means to appeal to others in FDA during an inspection?***

***A.*** There are both formal and informal ways to resolve a dispute with an investigator, through the ORA, the relevant product center, or elsewhere in FDA—depending on the nature of the dispute.

***Q. What is the significance of a 483? Are 483s public documents?***

***A.*** Technically, 483s do not have independent legal force. FDA states that a 483 "does not constitute a final Agency determination" of whether there has been a violation


of law. 4 FDA considers the 483, along with other evidence and documents and the firm's response, when determining whether compliance action is warranted.

However, FDA releases 483s under the Freedom of Information Act, upon request. If it believes that a 483 would generate significant interest, it may release the document proactively. FDA will redact protected information on 483s, such as trade secrets and commercial confidential information. The bottom line is that 483s will often become public and appear on the Internet, where they can affect the perception of, consumer confidence in and stock price of a company, even if there is no subsequent compliance action. Therefore, it is important for a company to raise objections and make its case before the investigator issues a 483.

***Q. If a firm receives a 483, what are the next steps for the firm?***

***A.*** A firm has 15 working days to respond in writing to a 483. If a firm believes that there is a clear factual error in a 483, it can ask FDA to amend the document. Because most observations on a 483 involve some degree of interpretation, however, the FDA rarely amends them.

A written 483 response can have a significant impact on whether FDA takes further compliance action. The 483 response should address all of FDA's observations. It should indicate which ones have been corrected already and provide a timetable and plan for correcting the others. The response can go beyond the specific observations and address the firm's overall corrective action plan and commitment to quality and compliance. A firm may request that FDA post the 483 response on FDA's website, if FDA has posted the 483.

1 Food and Drug Administration, *Investigations Operation Manual*, Chapter 5.2.3.
2 21 U.S.C. 374(a).
3 Food and Drug Administration, *Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection*, Oct. 2014.
4 FDA Form 483 Frequently Asked Questions https://www.fda.gov/iceci/inspections/ucm256377.htm.

***Q. If a firm receives a 483, what are the next steps for FDA?***

***A.*** The investigator prepares an Establishment Inspection Report (EIR), which provides substantially more detail than a 483. If the investigator took product or environmental samples, FDA will obtain laboratory analysis.

After the EIR is written, FDA will classify the inspection as No Action Indicated (NAI), Voluntary Action Indicated (VAI), or Official Action Indicated (OAI). The internal FDA process involves an ORA recommendation and, often, review by the applicable product center. An NAI inspection is often one in which the investigator did not issue a 483, though, sometimes, a 483 is issued, and, later in the process, FDA determines that the observations were not serious and classifies the inspection as NAI. VAI inspections may lead to inspection follow-up or more frequent reinspections, but typically no additional compliance actions. OAI inspections often lead to compliance actions for food and postmarket medical products and recommendations to withhold product approval for preapproval inspections.

After FDA has classified an inspection as NAI or VAI, it provides the firm with a copy of the EIR. For OAI inspections, firms do not receive the EIR until the relevant compliance action has been undertaken or the matter has otherwise been closed (such as with a decision to withhold product approval).

***Q. What types of compliance or enforcement actions does the FDA take?***

***A.*** FDA takes many different types of compliance or enforcement actions.

There are three types of judicial enforcement actions—the seizure of unlawful product; an injunction (usually ordering a firm to cease operations, abide by rigorous conditions or disgorge profits); and criminal prosecution. These actions usually involve companies that have had poor inspection histories; have, in FDA's view, caused a significant risk to public health; or have engaged in fraud or deliberate misconduct. The Department of Justice represents FDA in court. A criminal prosecution may occur even if FDA is also seeking a civil remedy.

FDA increasingly uses administrative enforcement tools, which vary by commodity. Under FSMA, FDA may issue administrative orders for the detention of product, mandatory recalls or the suspension of a company's registration (which has the effect of causing it to cease operations). In the device area, FDA may impose civil monetary penalties, order mandatory recalls and detain product. For drugs, FDA may detain product, but the other remedies are not available. FDA rarely pursues mandatory recalls because it will first indicate to a firm that it thinks that a recall is needed, and, if the firm refuses, FDA will post a strongly worded patient or consumer alert on the Internet. Firms usually agree to an FDA request to initiate a recall.

A powerful tool that FDA uses for imported products is Detention without Physical Examination, colloquially known as an "import alert." If it "appears" that there has been a violation of the Federal Food, Drug, and Cosmetic Act, FDA may bar import of the affected product.[5] FDA has used this authority to bar whole categories of product from a geographic area—for example, raw and cooked shrimp from India[6]—or from a specific company. FDA generally issues firm-specific alerts for medical products, but issues both firm-specific and geographic alerts for food. FDA employs import alerts when there is an imminent public health risk (usually coupled with a product recall), but also when there are long-term or systemic compliance problems. Products remain on import alert until FDA believes that the relevant compliance problem has been resolved. Most of the time, FDA believes that a reinspection is necessary before it

5 21 U.S.C. 381(a).
6 Import Alert 16-35 (https://www.accessdata.fda.gov/cms_ia/importalert_43.html).

lifts an import alert. When companies have corrected the problems that FDA has identified, they should proactively argue for the lifting of the import alert.

FDA frequently issues warning letters and untitled letters. Warning letters document serious compliance problems and warn companies that failure to correct the deficiencies could result in a more serious compliance measure, such as a judicial enforcement action. Firms have 15 working days to respond to a warning letter and describe the corrective actions that it has undertaken. It is important for firms to prepare thorough and timely responses, in consultation with outside technical and legal experts, as needed. FDA routinely posts warning letters on its website. FDA almost always conducts a follow-up inspection to verify that a company has taken appropriate corrective action. Untitled letters document less serious compliance issues. Although FDA does not post all untitled letters on its website, it releases them upon a Freedom of Information Act request.

### *Q. How long does FDA's compliance process take?*

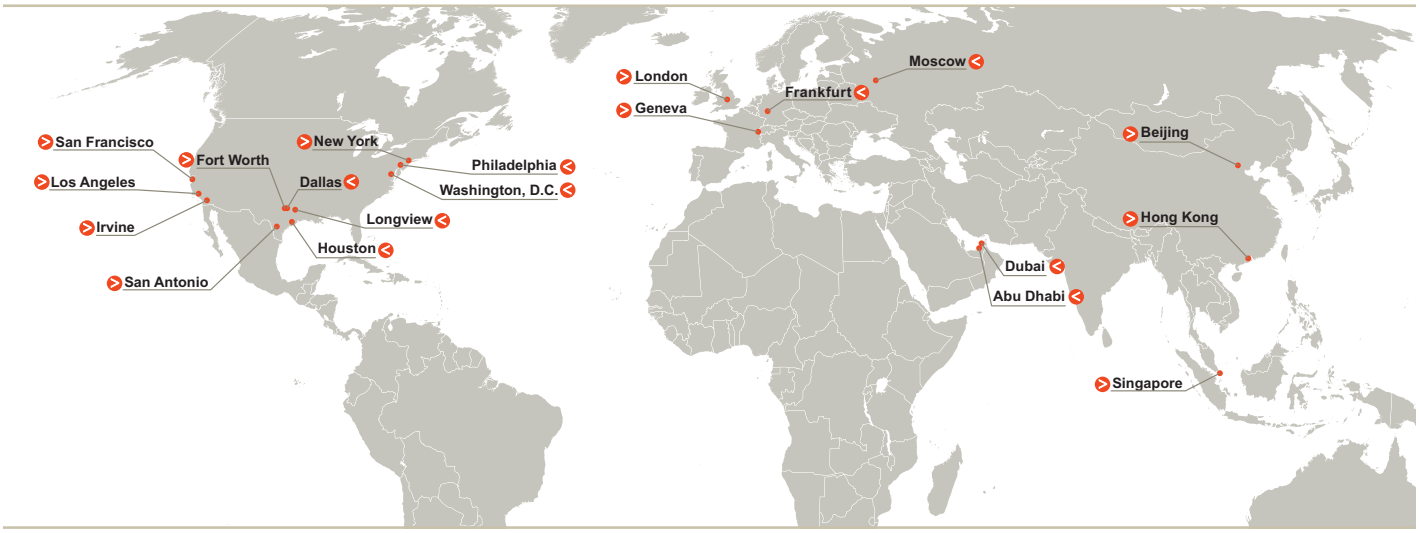
***A.*** When FDA believes that there is a public health emergency, it will act quickly. These situations typically involve FDA requests for a voluntary recall, mandatory recall, administrative detention or suspension of registration. If an import alert is meant to address an imminent risk, the FDA will issue it quickly. If it is a response to a more systemic concern, FDA's decision-making process may take weeks or months.

FDA sometimes issues warning letters and untitled letters many months after inspections. They are posted on the Internet rather quickly, making it important that firms be prepared to respond publicly. If time passes after a 483 response and a firm has still not heard from FDA, it should inform the agency of any material changes to its 483 response, such as additional corrective measures. During this quiet interval, a warning letter could be under consideration and new information could be pivotal.

The consideration of possible judicial actions by FDA and the Department of Justice is usually time-consuming, as are criminal investigations.

### *Q. Aside from the compliance actions mentioned above, if an FDA inspection produces a worrisome result, what other consequences should a firm anticipate?*

***A.*** The collateral consequences of a bad inspection depend on factors such as the risk to consumers and patients, whether product is contaminated and whether FDA uncovers fraud. Firms can be subject to tort and contract liability and investigations by Congress or state legislators. Foreign and state regulators and licensing authorities could take action based on FDA inspection results. Firms may also have to disclose inspection results and subsequent actions to shareholders. As soon as a firm anticipates troubling inspection results, it should consult counsel to evaluate next steps, not just with FDA, but in these other areas.

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