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Chapter 21

FDA Inspections

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§ 21:1 Role of Inspections

§ 21:1.1 Overview

U.S. Food and Drug Administration (FDA or the “Agency”) inspections are the Agency’s primary method of identifying regulatory violations. As such, they are vitally important to FDA regulatory and enforcement activities. Inspections also allow FDA to learn about industry trends, spot manufacturing or testing problems, and advise specific manufacturing, testing, or clinical facilities about how FDA believes generalized regulations apply to unique business models or products. They also play a starring role in almost every Warning Letter promulgated by FDA, and in almost every injunction proceeding or prosecution.

International inspections now play a more prominent role in FDA’s regulatory strategy, as the Agency seeks to monitor and control the hundreds of thousands of FDA-regulated medical, food, and cosmetic ingredients, components, and products imported for sale in the United States. FDA has expanded its presence abroad significantly in the past ten years (opening approximately nine offices in foreign countries since 2008), and the number of international inspections the Agency conducts has similarly increased, with the number of such inspections jumping by approximately 40% in 2014. FDA cooperates with certain foreign governments with regard to information on and inspection of certain facilities, but largely relies on its own resources with respect to international inspections.1

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§ 21:1.2 FDA’s Reasons to Inspect

There are many reasons that FDA may inspect a company, with inspections falling into three general categories: pre-approval inspections, routine inspections, and for-cause inspections.

FDA conducts pre-approval inspections before approving several categories of marketing applications, including New Drug Applications, Abbreviated New Drug Applications, PreMarket Approvals for medical devices, and premarking notifications (510[k]s) for medical devices. In these inspections, FDA reviews the entirety of the manufacturing process, including the manufacture of Active Pharmaceutical Ingredients, relating to the product that is the subject of the application to ensure that the facility or facilities in question are adequate and prepared to manufacture that product according to applicable regulatory requirements.

FDA conducts routine inspections of regulated entities on a risk-based inspection schedule. According to this schedule, the Agency conducts inspections of all regulated entities periodically, but more frequently where there is a greater risk of facility or product problems. This greater risk can be based either on the type of product at issue (that is, a sterile injectable product or a type of product prone to carrying certain pathogens) or the manufacturing facility’s history (that is, Warning Letters or past inspections that resulted in observations of violations). The FDC Act requires that drug manufacturing establishments be inspected generally once every two years; until recently, the average length of time for U.S. facilities averaged once every two or three years, and inspections of FDA-registered foreign drug manufacturing establishments averaged once every approximately thirteen years, unless the establishment was named in an application for a new drug.  

FDA also regularly inspects facilities and individuals who conduct clinical trials. Specifically, under the Agency’s Bioresearch Monitoring Program, FDA inspects clinical investigators, sponsors, monitors, contract research organizations, Institutional Review Boards, nonclinical (for example, animal) laboratories, and bioequivalence analytical laboratories. These inspections are intended to ensure the rights and safety of clinical research subjects, as well as to ensure the accuracy and reliability of clinical data that may be submitted to FDA in support of applications for product approvals.

FDA also conducts “for-cause” inspections, where the Agency has identified a problem (often as a result of a complaint from an employee

or former employee; occasionally as a result of a product recall or a complaint from a company's customers or competitors). Under these circumstances, FDA wants to investigate further, and potentially collect evidence to be used against the company in an enforcement proceeding. There is often some indication when an inspection is a "for-cause" inspection, but not always.

Routine inspections and "for-cause" inspections are the focus of this chapter.

§ 21:1.3 Potential Outcomes of Inspections

Sometimes the best a company can hope for after an FDA inspection is to avoid issuance of a Form FDA 483 ("483") (citing statutory and regulatory violations) or Warning Letter. However, inspections can have positive outcomes as well. For example, FDA may identify minor issues with the facility that can be quickly corrected during the inspection itself. By making such minor corrections, the company can demonstrate its commitment to compliance. The company also may have an opportunity to redeem itself in FDA's eyes if its previous inspection went poorly.

The negative consequences of a bad inspection can be substantial. If significant violations are observed, receipt of a 483 detailing those observations is inevitable. FDA may also issue a Warning Letter, initiate a seizure action or injunction proceeding, or, if the facility in question is located abroad, issue an import alert or detain products without physical examination. An import alert can stop all shipments into the United States from the facility in question, depending on the scope of the alert. FDA need not wait until it has issued a Warning Letter to the facility to put the facility on an import alert.

§ 21:2 FDA Authority to Access Facilities and Records and Conduct Interviews

§ 21:2.1 Generally

FDA's inspection authority under the FDC Act is broad. Section 704(a)(1) of the FDC Act, authorizes FDA officials to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce.
FDA’s inspection authority extends to equipment, materials, containers, and labeling in a facility within reasonable limits. FDA’s inspection authority also includes both finished and unfinished goods. While section 704 does not extend to inspection of records for all product categories, FDA has separate authority to request and inspect many facilities’ records. The extent of FDA’s authority to access records with respect to specific categories of regulated products (foods, drugs, devices, etc.) is discussed below in section 21:2.2.

FDC Act § 703(a) addresses FDA’s general authority to access records pertaining to “the movement in interstate commerce of any food, drug, device, tobacco product, or cosmetic, or the holding thereof during or after such movement, and the quantity, shipper, and consignee thereof.” That section authorizes FDA to access interstate shipping records. However, section 703 also requires FDA to make a request for the shipping records in writing, and must specify the nature or kind of food, drug, device, tobacco product, or cosmetic to which the request relates. Moreover, if FDA requests such records in writing, the documents provided in response to FDA’s request cannot be used in a criminal prosecution of the company that provides them. Accordingly, FDA’s practice is not to issue written requests pursuant to section 703.

The FDC Act reinforces FDA’s authority to conduct inspections by making it a violation of that Act—punishable by criminal, as well as a civil sanctions—to (1) refuse to permit access to or copying of certain records, (2) refuse to permit FDA to enter and inspect, or (3) fail to maintain certain records or make certain reports to the Agency. It is also a criminally actionable violation of U.S. law to knowingly make a false statement to FDA in the course of an inspection (or otherwise). As discussed below in section 21:2.5, FDA has published a Guidance document that elucidates the Agency’s position on what practices constitute a refusal to permit access.

The FDC Act and FDA regulations do not specifically authorize FDA to interview company employees (except for companies manufacturing biologic products). However, FDA inspectors often seek to conduct such interviews. With that in mind, it is advisable for companies to have a policy in place with respect to interviews. If the company chooses to permit employee interviews, it is advisable to require that the interviews be conducted in the presence of company counsel to safeguard privileged information.

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3. FDC Act § 704(a)(1).
4. Id. § 703(a).
5. Id. § 703(a).
6. Id. § 703(a).
7. See id. § 301(e), (f); 18 U.S.C. § 1001.
8. See 21 C.F.R. § 600.22(b).
§ 21:2.2  Authority with Respect to Specific Facilities

[A] Food and Dietary Supplement Facilities

With respect to food facilities, in addition to its general authority under section 704, FDA is also authorized to inspect and copy all records relating to the manufacture, processing, packing, distribution, receipt, holding, or importation of a food if (1) FDA has a reasonable belief that the food is adulterated and presents a threat of serious health consequences or death to humans, or (2) if FDA believes that there is a reasonable probability that use of or exposure to the food, and any other food that FDA reasonably believes is likely to be affected in a similar way, will cause serious adverse health consequences or death to humans or animals.9 The second category, in particular, facilitates FDA’s investigation of outbreaks of food-borne pathogens. Records requested under this authority must be made available as soon as possible, not to exceed twenty-four hours after receipt of the request.

FDA also has authority to access certain shipping records pertaining to the sanitary transportation of food.10 FDA has proposed regulations that set out the standards for sanitary transportation and the types of records that must be kept and made accessible to FDA upon request.11

With respect to dietary supplements specifically, section 761(e)(2) of the FDC Act authorizes FDA to access adverse event report records required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.12 FDA has also asserted that dietary supplement companies must allow FDA to inspect and copy all records required under the dietary supplement “Current Good Manufacturing Practice” regulations,13 including documentation of personnel qualification and training, records pertaining to facility and equipment maintenance and cleaning, documentation of the production and process control system [establishment of the system; requirements for quality control, master manufacturing records, batch production records, etc.]; and records pertaining to product returns and complaint handling.14 FDA’s authority to inspect and copy all these records is not specifically stated in the FDC Act.

Facilities that manufacture infant formula are also subject to additional FDA inspection authority. The Infant Formula Act of

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9.  FDC Act § 414(a).
10.  See id. § 416.
14.  See id. § 111.610.
1980\textsuperscript{15} created specific nutritional, quality, and good manufacturing control requirements for infant formulas, and mandated that companies make available to FDA all batch records, quality control records, nutrient test data and methodology, and similar documents, for examination and copying.\textsuperscript{16}

**[B] Drug and Biologic Facilities**

FDC Act section 704 authorizes FDA to access many of the records maintained by drug and biologic facilities (as well as certain device facilities, as discussed below) that relate to any potential violations of that FDC Act. Specifically, section 704(a)(1) states:

In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, the inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this chapter, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this chapter.

This broad records authority permits FDA access to the numerous records that could establish whether products are adulterated or mislabeled, which would include all manufacturing and testing records relating to the product or its ingredients. However, FDA is not authorized to access financial data, sales data (other than shipment information), pricing data, or personnel data (other than information on the qualifications of personnel to perform certain regulated functions), and certain research data.\textsuperscript{17} According to FDA policy, the Agency will not review reports of internal audits conducted pursuant to a company’s written quality assurance program.\textsuperscript{18}

The Food and Drug Administration Safety and Innovation Act (FDASIA)\textsuperscript{19} added to FDA’s inspection authority by authorizing FDA to request any documents that it is authorized to access under FDC Act section 704, “in advance of or in lieu of an inspection, within a

\begin{itemize}
\item \textsuperscript{15} Pub. L. No. 96-359, 94 Stat. 1190 (1980).
\item \textsuperscript{16} See FDC Act § 412.
\item \textsuperscript{17} Id.
\item \textsuperscript{18} See U.S. FOOD & DRUG ADMIN., INVESTIGATIONS OPERATIONS MANUAL § 5.6.2.2.
\item \textsuperscript{19} Pub. L. No. 112-144, 126 Stat. 993 (2012).
\end{itemize}
reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form.” 20

Specifically with respect to drug facility inspections, FDA has additional authority to penalize any delay, denial, limitation, or refusal of an inspection. Under FDC Act section 501[j], a drug is deemed adulterated if it is manufactured in an establishment that “delays, denies, or limits an inspection, or refuses to permit entry or inspection.” FDA has promulgated its interpretation of what constitutes a delay, limitation, denial, or refusal of an inspection in a guidance document.21 Importantly, the guidance document notes that delays, limitations, denials, or refusals to comply with an FDA request for records may also cause a manufacturer’s drug products to be deemed adulterated.22

[C] Device Facilities

Device facilities are subject to FDA’s general inspection authority.23 Device component facilities are covered by this authority as well, because the statutory definition of “device” includes components of devices.24 Moreover, while FDA is arguably limited under the statute to accessing only those medical device records contemplated by section 704, FDA regulations and policy statements indicate that FDA investigators generally assert authority to inspect certain other categories of records, such as records relating to the Quality System Regulation requirements, medical device reports, complaint handling, and corrections and removals [recalls].

As noted above in section 21:2.2[B], FDA is not authorized under FDC Act section 704 to inspect medical device financial data, sales data, pricing data, personnel data [other than the qualifications of technical and professional personnel performing functions subject to the FDC Act], certain types of research data, and shipping records [unless the FDA investigator provides a written request for shipping records that specifies the product to which the request applies]. Internal audit reports, as well as reports and memoranda on facility inspections, are also not subject to review or copying by FDA, by regulation. FDA investigators do not have the authority to access computer files, nor do they have the authority to ask that company employees search for emails or other communications, unless those

20. FDC Act § 704[a][4].
22. Id. at 5, 7–8.
23. FDC Act § 704.
24. Id. § 201[h].
communications fall into another category of documents that FDA is authorized to inspect.

[D] Cosmetic Facilities

Cosmetic facilities are subject to FDA’s general inspection authority. Thus, inspections of those facilities are conducted at reasonable times, in a reasonable manner, and without prior notice. FDA’s authority permits investigators to collect samples of cosmetic ingredients and finished product, as well as labels, packaging, etc. The inspector may also take swabs of equipment or other product-contact surfaces.

[E] Foreign Facilities

Foreign facilities that produce FDA-regulated products for sale in the United States, or ingredients or components of those products, are generally subject to FDA inspection authority. Unlike most inspections of domestic facilities, it was previously FDA’s policy that most inspections of foreign facilities were announced in advance. Recently, however, especially with the opening of FDA residence offices in foreign countries, many inspections are not pre-announced.

[F] Pharmacies

FDA is authorized to inspect retail pharmacies, including pharmacies that compound drugs, or “compounding pharmacies.” FDA takes the position that its authority to inspect pharmacies stems from its general authorization under section 704(a) of the FDC Act to enter the premises and conduct an inspection during normal business hours at any facility where drugs are processed, packed, or held. Because drugs are, at a minimum, “held” at a pharmacy, FDA has the right to inspect, although certain records maintained in the pharmacy are exempt from inspection as stated in FDC Act section 704(a)(2)(A). FDA is specifically authorized to inspect “at reasonable times and within reasonable limits and in a reasonable manner” the establishment, including all “pertinent” equipment, finished and unfinished materials, containers, and labeling.25

Section 704(a)(2)(A) of the FDC Act exempts pharmacy records from inspection where the pharmacy establishment is maintained in conformance with applicable local laws regulating the practice of pharmacy. Exempt pharmacies must be:

regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in

25. Id. § 704(a)(1)(B).
the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail.\textsuperscript{26}

Despite this explicit exemption for pharmacies, FDA has maintained that it is statutorily permitted to review documents traditionally considered subject to the pharmacy exemption to determine whether there is a violation of local pharmacy laws or section 503A of the FDC Act, or confirm that the exemption applies.

If a pharmacy objects in the first instance to a notice of inspection, and if FDA believes that the pharmacy is engaging in acts inconsistent with the FDC Act, FDA likely will be able to obtain a warrant from a court permitting FDA to enter the premises and inspect those documents and articles within the scope of the warrant.\textsuperscript{27}

FDA inspections of pharmacies registered as outsourcing facilities are governed by a specific statutory provision confirming FDA’s inspection authority.\textsuperscript{28}

\section*{\textsuperscript{21:2.3} Who Conducts an Inspection?}

In many cases, one or more FDA investigators conduct an inspection. However, FDA investigators can, in some cases, be accompanied by state officials or officials from other federal agencies such as the U.S. Department of Agriculture or the Federal Bureau of Investigation. In addition, FDA contracts with some states to conduct certain types of inspections, and in those states inspections may be conducted without an FDA official being present.

A company and facility’s relationship to its FDA inspector is a very important one. Not only is the inspector the conduit of factual information back to the Agency, but his or her overall impressions with respect to the company’s emphasis on compliance, its willingness to listen and make changes, its knowledgeability about legal requirements, etc., may influence Agency behavior toward the company for a lengthy period of time. Moreover, if the Agency were to bring any enforcement action (that is, for product seizure or for an injunction) against the company in court, the FDA inspector would likely be a star witness in that proceeding.

That said, it is important to understand how inspectors are trained. Many inspectors are trained to request records that companies may not be required to provide under the statute. Companies frequently

\begin{itemize}
  \item \textsuperscript{26} Id. § 704(a)(2)(A).
  \item \textsuperscript{27} See, e.g., Wedgewood Vill. Pharm., Inc. v. United States, 421 F.3d 263 (3d Cir. 2005).
  \item \textsuperscript{28} FDC Act § 503B.
\end{itemize}
comply with such requests in order to appear more forthcoming and cooperative, but they are not required to do so, and in some cases it may be more prudent to deny the request, citing company policy. For example, it may be prudent to deny a particular unauthorized request for records if the company is certain that FDA will pursue enforcement action regardless, and the inspection is simply an effort to update the Agency’s evidence in support of such action.

§ 21:2.4 FDA Credentials and Forms

Upon arriving to conduct an inspection, an inspector provides a Form FDA 482 [Notice of Inspection], as well as FDA official credentials [an identification badge]. An FDA official is not authorized to enter the facility and begin the inspection unless and until he or she presents these credentials.

If the FDA inspector deems it necessary because a facility has refused to provide certain records, or requests that FDA provide a separate written request for records [which, as discussed above, FDA rarely provides], FDA may issue a Form FDA 482c [Request for Records]. The inspector will document the fact that he or she was required to issue a Form FDA 482c, either because the facility refused to provide records or because it demanded a request in writing.

Additional inspection-related forms and documents include a 483 and an Establishment Inspection Report [EIR]. These are discussed below in section 21:5.2[A] and section 21:5.3, respectively.

§ 21:2.5 Refusal or Delay, the Definition and Consequences

As mentioned above, the FDC Act prohibits the delay, denial, or limitation of an inspection.29 Thus any refusal, delay, or limitation of an inspection is a crime. Moreover, drugs produced at a manufacturer that delays, denies, or limits an inspection may be deemed adulterated.30

In 2012, FDASIA authorized FDA to issue guidance concerning what constitutes refusing an authorized FDA inspection, which is a violation under FDC Act section 301[f]. The Final Guidance, published in October 2014, defines the various types of actions, inaction, and circumstances that FDA considers to constitute delaying, denying, or limiting an inspection, or refusing to permit entry or inspection for the purposes of FDC Act section 501[j].31 While the guidance only

29. FDC Act § 301[f].
30. Id. § 501[j].
purports to apply to drug facilities, it is written in terms that would appear to apply to all facilities subject to inspection pursuant to FDC Act section 704.

One of the most interesting features of the FDA guidance is FDA’s position that a facility’s refusal to permit the FDA inspector to take photographs will likely constitute a refusal or limitation of the inspection, unless there is a “reasonable explanation” (for example, the highly unlikely situation in which a camera flash is necessary and would negatively impact product quality).\textsuperscript{32} FDA also indicates that it expects a company to retrieve records from another facility when one facility is being inspected, which is an expectation that does not follow directly from any statutory text.\textsuperscript{33}

In addition, FDA’s guidance indicates that a facility may not, under usual circumstances, “send[] staff home for the day and tell[] the FDA investigator that the facility is not producing any product” at that time, because it would constitute “imped[ing] the investigator,” or even an outright refusal to permit observation of the manufacturing process, regarding which FDA argues that it has a right to “reasonable access.”\textsuperscript{34} This, in spite of the fact that the statute does not require employees to continue working, or to be made available, when an inspector arrives, and FDA’s guidance goes on to say that companies need not schedule manufacturing based on an investigator’s convenience.

\section*{§ 21:2.6 \textit{Involvement of State and Local Officials in Inspections}}

Many, if not most, states have enacted so-called “mini” FDC Acts, and some cities and localities have their own regulations governing foods, drugs, devices, and cosmetics. State and local officials have authority over a facility regardless of whether it ships product in interstate commerce. Thus, state and local officials may have concurrent or overlapping authority with FDA to inspect a facility under state law, or local ordinances and regulations. State and local authorities may occasionally inspect facilities in conjunction with FDA.

In preparation for a joint inspection, it is important to understand the state’s or locality’s authority to inspect your facility, as well as FDA’s authority to do so. Local officials likely have independent authority to collect samples of your product. Moreover, the state inspector may have a greater ability than FDA to take quick action against your product if it determines the product is adulterated or

\begin{thebibliography}{9}
\bibitem{32} Id. at 7.
\bibitem{33} Id. at 5.
\bibitem{34} Id. at 6.
\end{thebibliography}
misbranded, such as by imposing an immediate embargo (an authority that FDA lacks). If FDA requests that the state impose an embargo, the state authority will generally cooperate with FDA.

§ 21:3 Preparing for an Inspection

§ 21:3.1 Generally

There are a few key elements that should not be overlooked in preparing for an inspection. First, the facility must address any outstanding deficiencies or observations from its last FDA inspection. Even assuming the FDA inspector is a new one to the company or the facility, he or she will have researched the company’s and facility’s compliance history in advance of the inspection, and will be prepared to specifically inquire and determine whether and how the company has addressed past FDA observations. If a facility receives inspectional observations that are the same, or similar, to observations made in a previous inspection, FDA will refer to these observations as “repeat observations.” FDA is much more likely to respond to repeat observations with a Warning Letter or other enforcement action. Thus, repeat observations must be carefully avoided, and the FDA inspector will be specifically looking for such violations.

Second, the facility must address outstanding customer or user complaints, and the status of any ongoing corrective or preventive actions associated with its products. FDA is only in a facility for a short period of time, perhaps once every two or three years. Thus, FDA inspectors seek short-cuts to determining the potential underlying problems with a manufacturing facility or a product. Inspecting and analyzing complaints and a facility’s complaint-handling process is one such short-cut. Moreover, if an FDA inspector determines that a facility has multiple outstanding issues (or even one serious problem) requiring risk analysis, or preventive or corrective action that have been identified by the company, but not yet resolved, the FDA inspector will take note.

Finally, facility management should be sure to stay apprised of all recent developments in the law or FDA regulatory policy. Reliance on out-of-date FDA policies alone may be the cause of a negative inspectional observation.

§ 21:3.2 Policies

Each facility should have in place, and train employees according to, a Standard Operating Procedure (SOP) for FDA inspections. In addition to guiding the actions of company employees before and during an inspection, having written procedures provides a resource for employees in responding to common FDA requests and inquiries.
For example, rather than appearing argumentative by refusing to allow an FDA inspector to take video footage of the facility, an employee can point to the company policy that prohibits any individual from recording video footage on the premises.

An SOP should include guidance regarding escorting FDA investigators around the facility, and should identify a location where FDA investigators can inspect copies of requested documents. The SOP should also identify those company employees that are authorized to speak to FDA investigators, including the topics they are authorized to cover. It should identify whether and under what circumstances any employees should stop working or leave the premises during an FDA inspection, for legitimate manufacturing or business reasons. Finally, the SOP should address whether FDA interviews of company employees are permitted (as noted above, a company generally is not required to make employees available for interviews), and include policies regarding employee conduct during any such interviews. Policies should specify who is authorized to speak on behalf of the company, and that no employee should sign any affidavit or other document.

§ 21:3.3 Personnel

A company should define roles during inspections for key personnel, such as the Director of Regulatory Affairs, Quality Assurance Manager, or Production Manager. One individual should be identified as the primary point of contact for the FDA inspectors, in order to minimize the potential for miscommunication. In addition, a company should identify back-up for key personnel and the FDA point of contact, in case the primary individuals are out of town, sick, or otherwise unavailable when an FDA inspector arrives.

§ 21:3.4 Practice, Practice, Practice

Policies relating to inspections, while necessary, will be less than helpful if employees are not adequately trained to handle an inspection according to those policies. Formally training employees on the company’s written policies is vital. However, to ensure that employees can handle the stress of an inspection and respond according to policy, regardless of unexpected FDA questions or actions, nothing is more effective than conducting mock FDA inspections. Ideally, a facility will conduct two unannounced mock FDA inspections per year.

§ 21:4 During an Inspection

§ 21:4.1 Generally

During an inspection, it is important that one or two people be assigned to shadow the FDA inspector(s) throughout the day. An FDA inspector should never, or very rarely, be unaccompanied in the facility.
Record all FDA requests for documents and other materials, and make copies of all documents and materials provided to the FDA inspector. If the inspector requests samples of a particular product, be sure to retain sufficient quantities of that product—the same lot, and the same batch—to conduct reliable independent testing.

As noted above, FDA inspectors may request certain documents that the company is not obligated to provide, such as financial data, sales data (other than shipment information), pricing data, personnel data, or certain research data. An FDA inspector may also request documents pertaining to shipment in interstate commerce orally, rather than in writing, as required by the statute (and subject to certain protections). Whether to voluntarily provide some or all of these materials depends on the context of the inspection (so providing any general guidance for responding to such requests as discussed in this chapter would be imprudent).

In addition to requesting documents and materials, FDA inspectors also frequently try to take photographs or video of the facility, with or without requesting permission to do so. FDA has, for decades, claimed that its right to take photographs is inherent in the statutory authority to “inspect, at reasonable times and within reasonable limits and in a reasonable manner,” any facility and “all pertinent equipment, finished and unfinished materials, containers, and labeling therein.”

Recently, as discussed above in section 21:2.5, FDA published a final guidance document about what constitutes refusing an authorized FDA inspection, in which the Agency formally stated its belief that it is entitled to take photographs (the guidance document specifically addressed only drug facilities, but is likely to be applied more broadly), absent very unlikely extenuating circumstances. Rarely, FDA inspectors try to take video of a facility, and it seems inevitable that FDA would apply the same reasoning with respect to video as it does to photography. An FDA inspector is almost guaranteed to try to take photographs or video of (1) any evidence of a rodent or insect infestation, (2) faulty construction or maintenance of equipment facilities, (3) poor product storage conditions, or (4) visible contamination of raw materials or finished products. The inspector will also likely take photographs of product labels and labeling. As yet, no company has legally challenged an FDA inspector’s right to take photographs by refusing to allow photography.

§ 21:4.2 Questions and Answers

Throughout the inspection, and certainly at the end of each day, the company’s liaison should try to hold a mini close-out meeting of the day’s inspection, and should be prepared to answer questions posed by

35. FDC Act § 704(a).
the FDA inspector. However, we recommend against responding to FDA criticisms, unless the criticism is in writing or there is an excellent explanation that has no potential of raising other issues. Any response to a written FDA criticism should also be in writing.

Employees, including the primary FDA liaison, should be instructed that if they do not know the answer to a question posed by FDA or are uncertain, they should not answer, but should instead offer to get back to FDA with the answer. A carefully considered answer is preferable to an immediate off-the-cuff one, even if producing such an answer requires a minor delay. However, the delay in answering a question should not be more than one day unless the question is very complex. Employees should not solicit FDA inspectors for guidance about things they should know.

§ 21:4.3 Keeping a Record

In addition to documenting each of FDA’s questions and requests, as well as the documents and materials reviewed, samples taken, etc., facility management should prepare a summary of each day’s inspections. The summary should include FDA’s actions and statements, as well as the company’s own representations and actions with regard to the FDA inspector and in response to his or her questions and requests. Keep a record of any corrections that are made in response to FDA comments during the course of the inspection.

§ 21:4.4 Close-Out Meetings

At the end of an inspection, the FDA inspector[s] will conduct a close-out meeting with responsible individuals at the facility. At that meeting, the inspectors will discuss any violations they may have observed during the inspection and potential actions that the company could take to correct those violations. Unless no significant violations were observed, FDA in most cases will issue the company a 483, which details the Agency’s inspectional observations. At this point, it is unlikely that the company will be able to alter FDA’s decision to note the violations in question in a 483, which details inspectional observations. Thus, it is not recommended to discuss such observations orally with the FDA inspector. Nevertheless, company representatives should carefully note all of the inspectors’ recommendations, ask questions as necessary to clarify those recommendations, and prepare to respond to the 483 in writing. In general, 483s are not made public. However, upon request under the Freedom of Information Act (FOIA), FDA will release all portions of a 483 that do not disclose the company’s confidential commercial information.

After every inspection, FDA will also create an EIR, which summarizes the inspection and the Agency’s observations during that inspection, including any observations that may not have been deemed
significant enough to be included in a 483, and may also include key communications made by the company during the inspection. Like a 483, the EIR may become public, although confidential commercial information is redacted.

§ 21:5 Post-Inspection Follow-Up

§ 21:5.1 483 Response

[A] Generally

Many inspections result in FDA issuance of a 483, which notifies the inspected establishment of objectionable conditions relating to FDA-regulated products or processes, or of other potential violations of the FDC Act that were observed during an FDA inspection. However, it is important to note that these items are observations only, and do not constitute a determination by FDA that the facility is out of compliance. In fact, the 483 itself states that its contents are inspectional observations, and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA. 36

In practice, objections to any observations, and a discussion of corrective action, should be submitted to FDA in writing.

[B] Timeline

FDA generally allows fifteen business days for an establishment to provide a response to 483 observations. 37 While FDA has not made clear whether “business days” includes federal holidays, it is generally understood that “business days” means working days and, thus, does not include holidays. 38


37. See U.S. FOOD & DRUG ADMIN., INVESTIGATIONS OPERATIONS MANUAL § 5.2.7; Review of Post-Inspection Responses, 74 Fed. Reg. 40,211, 40,212 (Aug. 11, 2009) (announcing fifteen-day time limit enforcement program, to begin on September 15, 2009).

The fifteen-business-day deadline is firm, in that FDA may not consider responses received more than fifteen business days after the 483 was issued before determining whether to issue a Warning Letter. However, in some rare situations, FDA is willing to extend the deadline.

If FDA receives a response to the 483 within fifteen business days, but still decides to issue a Warning Letter, the Agency will consider and respond to the adequacy of the establishment’s corrective actions within the Warning Letter. However, if FDA receives a response more than fifteen days after issuance of the 483, it will only evaluate that response along with other written material the establishment provides in response to the Warning Letter.

[C] How to Address and Format Your Response

The 483 will include a name and address to which the 483 response should be addressed. This is usually the name and address of the FDA district director for the district in which a domestic establishment is located. In addition to a hard copy, the company should also provide FDA with an electronic copy of the response letter.

The 483 response should be organized according to FDA observation, and should address each observation, regardless of whether or not the company agrees that the observation was correct. The response may state disagreement, but should simultaneously address the observation in spite of that disagreement. The 483 response should include attachments evidencing corrective actions to date, and should have an index to all attachments. It should also include a chart identifying commitments that are ongoing and those that have been completed.

[D] Tips for Success

The most important thing to do in a 483 response is to demonstrate the fact that company management is taking the 483 observations seriously, and is committed to taking effective and expedient corrective actions. The response should specifically include management oversight as an aspect of each corrective action. It should also allocate sufficient resources to implement the corrective actions discussed, such as improvements to facilities or equipment, hiring additional personnel, or retraining existing employees.

With respect to each proposed corrective action, the 483 response should (1) provide an achievable timeframe for completion of the corrective action if it is not already complete; (2) provide a timeline that identifies critical milestones on the path to completing the corrective action; (3) provide objective evidence of the corrective action demonstrating that it has been, or is being, carried out; and (4) if needed, commit to providing FDA with process reports at regular intervals as the corrective action progresses. The 483 response should also include a
date by which the company expects that all corrective actions will be completed, if they are not already complete.

In addition to addressing completion of corrective actions with respect to each 483 observation, the 483 response should provide a means by which FDA can assess the success of corrective action and the likelihood of sustained compliance of that corrective action. That should include a discussion of how the company plans to evaluate the effectiveness of its own corrective actions. For example, the company may commit to increasing its internal or third-party audits following completion of the corrective actions.

Finally, as a general matter, a 483 response should address the 483 observations on a systemic level, rather than addressing isolated incidents. For example, if there is a specific 483 observation regarding the handling of a particular complaint, the company must go beyond resolving the issues with regard to that complaint and address the potential underlying reason(s) that the complaint was mishandled in the first instance. In our example, this could require a retrospective review of all complaints handled within a certain period of time.

§ 21:5.2 Close Out and the Establishment Inspection Report

When FDA considers an inspection to be “closed” it will release a copy of the EIR to the inspected establishment. FDA defines closed by regulation, at 21 C.F.R. § 20.64(d)(3). Specifically, the Agency views “[t]he consideration of regulatory enforcement action based upon a particular record” as closed when (1) a final decision has been made not to take an administrative action, or an administrative action has been taken and the matter has been concluded, or (2) a final decision has been made not to recommend a court action to a U.S. Attorney, or a court action has been instituted and all related appeals have been concluded, or the statute of limitations runs. In view of that relatively narrow definition of “closed,” it can be a very long time before a company is able to receive its EIR.

When the inspection is ultimately “closed,” and the EIR released, only the narrative portion of the EIR is released to the inspected establishment. Attachments and exhibits are not released.

§ 21:5.3 Publicity

Upon close of an inspection, FDA will automatically provide the inspected establishment with its EIR. However, both the EIR and 483 associated with the inspection are also subject to FOIA requests by the public. Some publishing and other companies routinely request all 483s and EIRs issued within a particular time period, and FDA will release those upon request, although it will redact the inspected
establishment’s confidential commercial information. Depending on the severity of observations contained in a 483, the 483 may garner significant media attention, as well as attention from investors, etc.

§ 21:5.4 Warning Letter Response

[A] Generally

FDA will generally issue a Warning Letter following an inspection where (1) the violation observed during an inspection rises to a level of regulatory significance; and (2) FDA has determined that the company’s written response to the 483 observation(s) is inadequate to address the violation. A Warning Letter serves multiple regulatory purposes from FDA’s perspective. First, it gives the company an opportunity to voluntarily correct the violation(s) in question, while raising the stakes for the company if it should fail to do so. Second, because Warning Letters are generally publicized by the Agency, they serve as guidance to the rest of the industry regarding FDA’s policies and expectations. Third, a Warning Letter satisfies FDA’s general policy of providing “prior notice” to companies before taking any further enforcement action (unless the particular circumstances warrant taking enforcement action in advance of any warning).

In some cases, rather than provide a Warning Letter to a foreign company as a result of an inspection and inadequate 483 response, FDA will simply place that company’s product on import alert. The import alert will keep all products subject to that alert from being imported for sale in the United States until the company addresses FDA’s concerns raised by the inspection.

Unlike 483s, which usually must be the subject of a FOIA request before they are made public beyond the receiving establishment itself, FDA Warning Letters are automatically and sometimes almost immediately published on FDA’s website. In some cases, the Agency will issue a press release discussing the Warning Letter, either individually or as part of a group of Warning Letters that have been sent.

[B] Timeline

The Warning Letter itself will set out a time period within which the recipient is expected to respond. In general, FDA will give a Warning Letter recipient fifteen working days to respond after receiving the letter. As is the case with a 483 response, FDA may choose not to consider any response it receives after the fifteen-day deadline, as it decides whether to take further enforcement action against the company. Also similar to a 483 response, FDA may in some circumstances be willing to consider granting an extension beyond the fifteen-day time period.
[C] How to Address and Format Your Response

Each Warning Letter provides a contact name and address to which the recipient should direct any response. Depending on the exact circumstances, a recipient may want to consider carbon copying other individuals or offices at FDA on its response. For instance, it may be helpful to copy the ombudsman’s office if the company has been communicating with the ombudsman with respect to related issues, or the Office of Chief Counsel if the company has significant legal objections to the content of the Warning Letter.

[D] Tips for Success

Many of the practices recommended for a 483 response also apply when a company is responding to an FDA Warning Letter. Again, demonstrating the company’s serious commitment to addressing the violations at issue is the foremost goal of a Warning Letter response. Again, the adequacy of documentation, resources committed, management oversight, and concrete milestones are key elements in a Warning Letter response.

Although it may end up being very similar to the company’s 483 response, a Warning Letter response should tell a complete story in and of itself, without reliance on any other submissions the establishment may have made to FDA. For this reason, there will likely be significant repetition between an establishment’s 483 response and the Warning Letter response. Moreover, the company may need to resubmit information that it provided to FDA after its initial 483 response, but before receiving the Warning Letter (for example, periodic update reports that were sent to FDA pursuant to a plan set out in the 483 response). The company’s Warning Letter response should refer specifically to the dates and contents of all communications it has provided the Agency detailing its response to the violations at issue, and all other contacts it has made with FDA in an attempt to resolve the violations.

A Warning Letter response differs in some respects from a 483 response. Importantly, receipt of a Warning Letter means that FDA officials have reviewed the inspectional findings in the 483 and have determined that serious violations exist. Thus, the company is in a much more defensive position. As such, the company should be sure to state any legal basis for objection to the violations alleged in FDA’s Warning Letter. Another reason to take a more defensive tack in a Warning Letter response is the fact that a Warning Letter is likely to have been more widely publicized. Thus, the company’s response (which will also become public, with the exception of confidential commercial information, at some point) should be directed at FDA, but with awareness that there is a larger public audience for that response.
Either in its Warning Letter response, or after submitting that response, a company may want to request a meeting with FDA to follow up and discuss the response. If FDA grants a meeting, FDA representatives may convey during that meeting whether the Agency was satisfied with the response (in which case FDA likely will reinspect the establishment to confirm corrections and improvements) or find that response to be inadequate (in which case the Agency will likely pursue additional enforcement action).
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