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FDA Enforcement— Facility Inspections

Alena C. Galante & Michael F. Ruggio

This chapter provides an overview of FDA terminology and the basics of facility inspection. Questions are presented from the company perspective with regard to what can be refused, questioned, and stated. Since most companies are global, foreign inspections are mentioned.

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FDA Inspection Basics

Q 2.1 What does FDA inspect?

FDA inspects manufacturers or processors of Food and Drug Administration (FDA)-regulated products to verify that they comply with relevant regulations. Those inspected include:

- vaccine and drug manufacturers;
- blood banks;
- food processing facilities;
- dairy farms; and
- animal feed processors.

FDA also inspects:

- facilities that conduct studies in people (clinical trials);
- laboratories that conduct studies in animals or microorganisms when these studies are used to apply for FDA approval of a medical product;
- foreign manufacturing and processing sites for FDA-regulated products that are sold in the United States; and
- imported products at the border.¹

Q 2.2 When does/can FDA inspect an establishment/firm/company?

FDA inspects manufacturers or processors of FDA-regulated products after an application is submitted to FDA for a new product; when a

facility is due for a “routine” inspection or as a follow-up to a previous inspection (for example, typically once every two years); or to investigate a specific problem that came to FDA’s attention. As mentioned above, inspections include foreign manufacturing or processing sites for FDA-regulated products that are sold in the United States.

Q 2.3 What are the types of inspection?

FDA conducts a **pre-approval inspection** of a facility and the drug manufacturing process in order for the company to market the new product. FDA conducts a **routine or general inspection** to ensure that manufacturing facilities remain in compliance with federal regulations. FDA conducts a **“for-cause” inspection** to investigate a problem that was brought to the attention of FDA.

Q 2.4 Can the company refuse an inspection?

Yes. A company can refuse an inspection or access to any area or record, but the company needs to recognize that in order to manufacture drugs for distribution in the United States (ignoring vitamins and nutritionals, which are considered foods and subject to different rules), a company must hold a license. That license is predicated on conformance to the Federal Food, Drug, and Cosmetic Act (FDCA), and, more specifically, Title 21, Part 211 of the Code of Federal Regulation, which is FDA’s mandate to inspect. If the company refuses an inspection, FDA has the right to terminate the license, which is a more drastic measure than recall, seizure, and injunction—all of which permit the company some measure of operational capability. If the company were to refuse access to an inspector, FDA can get a court order and force their way into the facility, accompanied by U.S. Marshals, to see what they wish to.

The Inspection

Q 2.5 How should an onsite inspector visit be handled?

The company should have standard operating procedures (SOPs) on handling FDA inspections. The SOPs shall address the notification of key company employees when an inspector arrives at the door.

The SOPs shall also address who will and how to interact with the inspector(s) as well as the responsibilities of these key personnel, so that employees who are designated to host and accompany FDA inspectors shall be knowledgeable about site operations and how to appropriately work with regulatory authorities. The site manager is usually designated as the recipient of the inspection notice.

A designated location, such as a conference room near the building entrance, shall be identified. Inspector(s) typically remain in the designated conference room, except for personal breaks and if they request a tour of the facility. The inspector(s) may be consulted on the proper protocol for them when it comes to providing drinks, snacks, or meals. Typically, FDA inspectors prefer to purchase their own drinks, snacks, or meals, and may even want to do so offsite.

The SOPs on handling inspections shall also identify processes for obtaining requested information, recording and tracking of requested documents and copies, documenting inspection activities each day and distribution of this information, and follow-up and response procedures once the inspection concludes. The SOPs shall also identify site activities that are permitted and suspended during the inspection time period.

Q 2.6 Who does FDA see—Legal, Quality, or Management?

At the beginning of the inspection, FDA typically requests an overview of the site and asks for organization charts. They may request to speak with anyone in the organization, but usually leave it up to the company to identify the expert who can best answer the inspector's questions. It is typical for Quality Assurance to host FDA inspection, and for representatives of Validation, Quality Control, Production, Engineering, and any other departments that are involved with manufacturing of product to participate as required in the inspection process. Ultimately, the appropriate company representative will depend on the reason for the inspection and the inspector's path of questions.

Q 2.7 What documentation is subject to inspection?

Documentation subject to inspection includes any record that FDA is entitled to have access to or copies of under the FDCA. Typically, this is documentation that supports the product's life cycle (for example, production records, product stability studies, packaging material studies, analytical methods, equipment qualification studies, etc.). However, FDA authority does not include access to certain information such as product formulas, shipment lists, codes, etc., unless specifically required by law.

Q 2.7.1 How should a company handle an inspector request to review records that are not subject to inspection?

The company should ask the inspector to provide the specific reference in the law that lists the record in question. If the inspector cannot provide the reference, then the company can refuse. The inspector will make note of the refusal.

Q 2.8 Does the company have to provide deviations, change controls, complaints, and rejected batches in an electronic format rather than just paper?

There is no requirement for the format of copies to be provided to FDA nor any guidance that states records must be provided in both paper *and* electronic format. However, if data exists as electronic data, then FDA may request a copy.

Q 2.8.1 Does the company have to grant FDA access to "live" demos of their systems?

FDA should not personally access a company's electronic records, databases, or source/raw data during the course of the inspection. The integrity of the data must be maintained and unauthorized changes must be prevented. FDA is required to verify that the data is original and authenticate the copy they receive, so FDA may observe an employee accessing the database/system that contains the requested information and the action of copying the data.

Q 2.9 If there are specific requirements in site SOPs (no cosmetics, for instance) to which inspectors are unwilling to conform, can access be denied to those areas?

Yes. The inspectors must comply with specific requirements, such as gowning procedures in order to enter production areas. The company should ensure that the appropriate escort, training, clothing, lockers, etc., are available to assist the inspectors.

Q 2.9.1 If an inspector comes to the site during non-business hours, is the company obligated to bring in the appropriate personnel?

The company has the option to refuse the inspector. Make certain to explain the reason for the refusal; the inspector is required to document the refusal. The company also has the option to allow the inspector on site during non-business hours, and it is at the company's discretion whether or not to bring in certain personnel. The company can better determine its options if it knows the inspector's reasons for coming during non-business hours and the line of questioning involved.

Q 2.10 How should a company handle an inspector whose questions are outside the scope of the inspection?

If an inspector begins to ask questions outside the scope of the inspection, which is noted on Form FDA 482, Notice of Inspection upon arrival, the company may point that out to the inspector and refuse to answer.

Q 2.10.1 If an adversarial relationship develops during an inspection, is there an opportunity to replace the inspector?

The company should do its best to diffuse the situation and proceed with diplomacy, honesty, and tact. However, should a situation escalate to the point where the inspection process is impeded, the company can request to stop for the day. The company may contact

the inspector's supervisor and report the situation. The supervisor will advise on how the inspection will proceed.

Q 2.10.2 Does a company have the right to refuse permission to take photographs during an inspection?

The general consensus has long been that a company could deny an FDA inspector the right to take photographs of their facility absent a warrant documenting the need for such access. Although FDA has long expressed the opinion that the provisions of section 704 of the FDCA² provided agency inspectors with the right to take photographs as part of the inspection process, few if any challenges were made in the face of a refusal by companies.

The passage of the FDA Safety and Innovation Act (FDASIA) in 2012 authorized FDA to issue a guidance as to what constitutes a refusal to allow an inspection, thus subjecting the company to criminal sanctions under section 301(f).³ A draft guidance was finally issued in July 2013 (made final in 2014) that specifically addresses the issue and clearly states that photographs are an integral part of an FDA inspection “because they present an accurate picture of facility conditions.”

To date, there have been no legal challenges either by companies or FDA. An argument could be made that where the conditions of the site are not an issue (for example, reviewing internal documents to determine if filings with the agency were made in a timely manner), taking photographs may be considered unnecessary and beyond the scope of the inspection process.

Post-Inspection

Q 2.11 What are the possible results of an inspection?

A *Form FDA 482* is the Notice of Inspection that is delivered at the time of arrival on site. It states the intent of the inspection (for example, general inspection, pre-approval inspection for a new product, etc.).

Following the inspection, if there are any deviations found from the regulations, FDA issues a *Form FDA 483* to the company. This form lists the specific non-conformances to current Good Manufacturing Practices (cGMPs) and the details of the documentation reviewed that drew them to their conclusion. A response to the 483 is expected from the company. The response should address each observation by providing an explanation, corrective actions to be taken, and a timeline for those corrective actions, or by asking for clarification. If the company disagrees with the observation, then the company should state so and provide the justification. A timely response to the Form FDA 483 is a good idea to prevent, in some cases, the issuance of a Warning Letter.

A *Warning Letter* may be issued to a company that is in violation of regulations and may warrant enforcement action. The intent of the Warning Letter is to provide the company the opportunity to take voluntary and prompt corrective action to avoid any enforcement action by FDA, such as withholding product approval or shutting down a plant.

If no action is taken by the company or FDA is not satisfied with the proposed action, then the company may be put under the order of a *consent decree*. A consent decree legally forces the company to bring its products, processes, and/or facilities into compliance with regulations under the supervision of FDA. A consent decree often requires the company to hire a third-party expert to thoroughly audit its facilities and internal procedures, and assist with the implementation of new procedures and controls.

Q 2.11.1 If the company disagrees with an observation, or believes it is incorrectly stated, what are the company's options?

The inspectors should discuss all observations with the company management as they are observed, or on a daily basis, to minimize surprises, errors, and misunderstandings when the Form FDA 483 is issued. This discussion should include those observations that may be written on the Form FDA 483 and those that will only be discussed

with management during the closeout meeting. The company may use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made during the inspection process. Inspectors are encouraged to verify the company's completed corrective actions as long as the verification does not unreasonably extend the duration of the inspection.

Once the Form FDA 483 is issued, the company must respond. The company may request clarification, criticize 483 items, disagree with the 483, or raise other questions or issues. In these cases, the FDA District Office will evaluate the company's information and send the District's conclusion to the company. A copy shall also be sent to the official establishment file.

Q 2.12 Why are U.S. firms inspected without notice?

Pre-announcement of an inspection is only given to those establishments that meet specific criteria and, using clearly described criteria, is done at the discretion of the inspecting office. The pre-announcement should be no less than five days in advance of the inspection. The company is expected to meet the expectations of having the appropriate personnel and records available for the inspection.

The following types of inspections are applicable for pre-announcement: pre-market inspections (such as 501(k) Premarket Notification and Premarket Approval (PMA)); foreign inspections; and Quality System/GMP inspections for biennial routine inspections, initial inspections of new facilities, or newly registered companies; and initial inspections under new management and/or ownership. The criteria used to determine applicability is (1) non-violative Quality System/GMP inspection histories; and (2) to remain eligible for pre-announced inspections, companies must have a history of having individuals and/or documents identified in previous pre-announced inspections reasonably available at time of the inspection.

Non-FDA Regulations

Q 2.13 If an inspector has seen a certain practice in one company does he/she have the right to mandate adoption to others?

FDA inspects to ensure compliance with existing and approved regulations. If there are practices observed in other previously inspected companies that FDA believes have resulted in raising the bar for the industry, then FDA may inform the current company of the better practices and suggest that it follow suit. This is a difficult position for the company to be in if it feels that it is complying with regulations and using an acceptable method or process. It should be noted that it is important for a company to participate in industry meetings and discussions as they pertain to new practices and regulations. There is nothing stopping FDA from withholding product approval if, for example, it has reason to believe that the company is not doing all that it can to be in alignment with current standards.

Foreign Complaints

Q 2.14 Can FDA enforce compliance on a company for issues/complaints that did not originate in the United States?

Yes. For example, FDA can enforce Food Additive Regulations or Biological Product Deviation Reports complaints on a U.S. company even if the origination of the complaint was from a foreign jurisdiction.

Notes to Chapter 2

1. U.S. FOOD AND DRUG ADMINISTRATION, ABOUT FDA, www.fda.gov/AboutFDA/Transparency/basics/ucm194888.htm.
2. 21 U.S.C. § 374(a)(1)(B).
3. 21 U.S.C. § 331(f).

