
Guidance for Industry Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection

**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs (ORA)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

October 2014

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Guidance for Industry¹

Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) was signed into law. Section 707 of FDASIA adds 501(j) to the Food, Drug, and Cosmetic Act (FD&C Act) to deem adulterated a drug that “has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection.” Section 707(b) of FDASIA requires the Food and Drug Administration (FDA) to issue guidance that defines the circumstances that would constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection, for purposes of section 501(j).

This guidance covers facilities that are subject to inspection under section 704 of the FD&C Act.² This guidance defines the types of actions, inaction, and circumstances that the FDA considers to constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection for the purposes of section 501(j).³ The examples used in this guidance are not intended to serve as an exhaustive list; rather, they illustrate the most common situations that FDA has encountered in preparing for and conducting inspections as well as situations that FDA anticipates may occur. FDA does not interpret the four terms describing prohibited behavior (delay, deny, limit, refuse) necessarily to be mutually exclusive. Therefore, the behaviors

¹ This guidance has been prepared by Office of Regulatory Affairs (ORA) in cooperation with Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Veterinary Medicine (CVM) at the Food and Drug Administration.

² The guidance therefore covers facilities subject to inspection under any of the authorities in section 704 of the FD&C Act, even if some other authorities in that section may be limited or inapplicable. For example, it covers a pharmacy subject to inspection under the first sentence of section 704(a)(1) even if the third sentence of section 704(a)(1) is not applicable because of section 704(a)(2).

³ This guidance describes actions or inactions that may cause a drug to be adulterated under 501(j). Actions or inactions that cause a drug to be adulterated under 501(j) may also violate other provisions of the FD&C Act or other federal or state laws. Furthermore, actions or inactions for which a facility provides a reasonable explanation and therefore would not cause a drug to be adulterated under 501(j) may nevertheless violate other provisions of the FD&C Act or other federal or state laws.

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described in the following scenarios may be examples of more than one type of prohibited behavior. Also note that, for purposes of this guidance, the term facility is intended to include all establishments, factories, and warehouses covered by section 501(j).

Section 704 of the FD&C Act authorizes FDA to conduct inspections at reasonable times, within reasonable limits, and in a reasonable manner. Although the FD&C Act does not specifically define “reasonable,” FDA has long maintained that the inspectional authority under Section 704 of the FD&C Act “extends to what is reasonably necessary to achieve the objective of the inspection.”⁴ FDA intends to work with facilities to conduct inspections and procure the information necessary to achieve the objective of the inspection. FDA will consider reasonable explanations for behavior that may otherwise be considered to be delaying, denying, limiting, or refusing an inspection.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 704(a) of the FD&C Act provides FDA authority for inspections, specifically providing authority for duly designated officers or employees of the FDA to enter, at reasonable times, and inspect, at reasonable times and within reasonable limits and in a reasonable manner, facilities subject to regulation under the FD&C Act.⁵ An FDA inspection is a “careful, critical, official examination of a facility to determine its compliance with certain laws and regulations administered by the FDA.”⁶ Section 706 of FDASIA amended section 704(a) of the FD&C Act

⁴ FDA, Investigations Operations Manual, Section 2.2.1.1, Authority to Enter and Inspect (2014).

⁵ Section 704(a) (21 U.S.C. 374(a)) authorizes “officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge...to enter, at reasonable times, any factory, warehouse, or establishment in which... drugs... 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... drugs... in interstate commerce; and... to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein.... In the case of any factory, warehouse, establishment or consulting laboratory in which prescription drugs, [and] nonprescription drugs intended for human use,... 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, [and] nonprescription drugs intended for human use... are adulterated or misbranded within the meaning of this Act...” Courts have upheld the legality of such an inspection if it is conducted at a reasonable time, within reasonable limits and in a reasonable manner. See United States v. Biswell, 406 U.S. 311 (1972); United States v. Del Campo Baking Mfg. Company, 345 F. Supp. 1371 (D. Del. 1972); United States v. Business Builders, Inc., 353 F. Supp. 1333 (N.D. Okla., 1973); see also FDA, Compliance Policy Guide, Section 130.100, Inspectional Authority; Refusal to Permit Inspection (Oct. 1, 1980).

⁶ FDA, Investigations Operations Manual, Section 5.1.2, Inspectional Approach (2014). Information collected by FDA during an inspection may contain trade secrets, confidential commercial or financial information, personal information, or other information that is exempt from public disclosure under the Freedom of Information Act, 5

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by adding 704(a)(4), which allows FDA to request, in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, records or information that FDA may inspect under section 704(a).

Facilities that are required to register under section 510 of the FD&C Act⁷ and that voluntarily register as outsourcing facilities under section 503B of the FD&C Act⁸ are required to submit certain information to FDA. FDA uses registration information for many purposes, including scheduling inspections. It is imperative that drug facilities register under section 510 when required, and that all registered facilities provide the information required by statute and our regulations to avoid creating confusion or complicating the scheduling and conduct of inspections. We also strongly encourage facilities to update point of contact e-mail information submitted to the Agency promptly if a change occurs after an annual registration submission.⁹

It is a prohibited act under sections 301(e) and 301(f) of the FD&C Act to refuse to permit entry or inspection or refuse to permit access to or copying of certain specified records.¹⁰ New section 501(j) of the FD&C Act, as added by FDASIA section 707, now deems a drug to be adulterated if "...it has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection."

III. DELAY OF INSPECTIONS

Delays may occur for many reasons, some of which are beyond the control of the facility. However, where an owner, operator, or agent causes the delay of an inspection, this may cause the drugs to be adulterated under section 501(j) of the FD&C Act.

A. Delay Scheduling Pre-announced Inspections

The FD&C Act does not require FDA to pre-announce its inspections. Therefore, FDA usually does not pre-announce for-cause and routine surveillance inspections. It is, however, FDA's

U.S.C. 553, or is protected from disclosure by other federal laws. See, e.g., 21 U.S.C. 331(j), 18 U.S.C. 1905; see also 45 C.F.R. 5.65, 21 C.F.R. 20.61.

⁷ See also 21 C.F.R. 207. For additional information, see Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing.

⁸ In December 2013, FDA issued draft Guidance for Industry, Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.

⁹ Some facilities subject to inspection under section 704 of the FD&C Act, such as compounding pharmacies, may not be required to register under section 510 because they fall within an exception in section 510(g) and may not have elected to register as outsourcing facilities. Such facilities are not required to provide a point of contact e-mail address to FDA, but the Agency may refer to a point of contact designated in a state license in preparing for inspections or for other purposes, and we therefore encourage such firms to ensure that any point of contact provided in a state license is valid.

¹⁰ Section 301 (21 U.S.C. 331) provides in pertinent part: "The following acts and the causing thereof are hereby prohibited: ... (e) The refusal to permit access to or copying of any record as required by section... 704(a) (f) The refusal to permit entry or inspection as authorized by section 704." Section 303 (21 U.S.C 333) provides penalties for violations of Section 301.

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general practice to contact the firm before an investigator arrives at the inspection site for pre-approval and pre-license inspections, and most inspections of foreign facilities of drug products. This pre-announcement, although not required, is intended to facilitate the inspection process and ensure that appropriate records and personnel will be made available.

FDA's efforts to schedule pre-announced inspections include sending correspondence to the facility's point of contact e-mail address, including the facility's U.S. agent if the facility is a foreign facility. FDA will make reasonable accommodations for local conditions, such as weather or security situations, holidays, and other non-work days, and, where appropriate, scheduled manufacturing campaigns. Examples of delay in scheduling a pre-announced inspection that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- A facility will not agree to a proposed inspection start date and does not give a reasonable explanation for its failure to do so.
- After scheduling an inspection, a facility requests a later start date without giving a reasonable explanation.
- A facility fails to respond following FDA's attempt to contact the facility's designated contact(s).

An example of a potentially reasonable explanation that might result in the drugs not being deemed adulterated under section 501(j) of the FD&C Act includes, but is not limited to:

- Manufacturing at the facility is not on-going, for example running only one manufacturing campaign per month and the facility requests a different date than that proposed by or agreed to by FDA so that manufacturing will occur during the FDA inspection of the facility.

B. Delay During an Inspection

An FDA inspection is intended to enable the Agency to review a facility's compliance with certain laws and regulations. In a drug facility, FDA has broad authority to inspect things that bear on whether the drugs are adulterated, misbranded, or are otherwise in violation of the FD&C Act. Actions by a facility's owner, operator, or agent before or after the beginning of an inspection that impede an FDA investigator at the inspection site from performing the inspection in a reasonable manner may be considered delaying the inspection. FDA is aware that its appearance on-site may initially cause some minor confusion and/or inconveniences to the facility's employees. Minor delays that result from good faith efforts by the facility to comply with FDA requests generally would not be considered unreasonable. Examples of delays during an inspection that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- A facility does not allow the FDA investigator access to an area of the facility until a specific future date or time even though the area is operational and is an area of the inspection site that FDA has authority to inspect, without giving a reasonable explanation.

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- A facility leaves the FDA investigator in a conference room without access to necessary documentation or responsible individuals for an unreasonable period of time that interferes with the investigator's ability to complete the inspection.

An example of a potentially reasonable explanation that might result in the drugs not being deemed adulterated under section 501(j) of the FD&C Act includes, but is not limited to:

- A facility does not provide the FDA investigator access to aseptic processing areas until the investigator accommodates the facility's documented gowning procedures.

C. Delay Producing Records

A critical aspect of FDA's preparation for inspection and inspection of drug facilities is the review and collection of hardcopy and electronic records, files, and papers bearing on whether the drugs are adulterated, misbranded, or are otherwise in violation of the FD&C Act. For example, records may be reviewed to verify compliance, but may also need to be collected to document evidence of deviations, interstate commerce, product labeling and promotion, and to identify the party or parties responsible for a variety of actions. Although FDA recognizes that facilities require a reasonable amount of time to produce records requested, especially if the records are maintained at a different site, a delay in producing records to FDA without reasonable explanation may be considered delaying the inspection. Examples of delays in producing records that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- During an inspection, the FDA investigator requests, within a specific, reasonable timeframe, records that FDA has authority to inspect, but the facility fails to produce the requested records within the timeframe requested by FDA, without reasonable explanation.
- FDA requests records pursuant to section 704(a)(4) of the FD&C Act, but the facility fails to produce the requested records in a timely manner, without reasonable explanation.

Examples of potentially reasonable explanations that might result in the drugs not being deemed adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- The FDA investigator requests translation of the records into English, and the translation is not readily available.
- The records requested are not available at that time because they are being used for a manufacturing operation that is in progress.
- The volume of the records requested is sufficiently large as to require reasonable time to compile.

In instances where the facility provides a reasonable explanation for delaying production of records, the facility should also ensure that the resulting delay is of a reasonable duration.

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IV. DENIAL OF INSPECTION

FDA interprets the word deny to include active behavior by the owner, operator, or agent of a drug facility to prevent an authorized representative of the FDA from conducting an inspection or to prevent FDA from completing an inspection. This includes statements or physical actions intended to avoid inspection or to mislead, deceive, or impede the investigator. Examples of behavior that may constitute a denial that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- A facility rejects FDA's attempt to schedule a pre-announced inspection.
- Upon arrival at the facility, the facility does not allow the FDA investigator to begin the inspection.
- A facility does not allow the FDA investigator to inspect the facility because certain staff members are not present, without a reasonable explanation.
- A facility does not allow the FDA investigator to inspect the facility by falsely alleging the facility does not manufacture, process, pack, or hold drugs.
- A facility sends staff home for the day and tells the FDA investigator that the facility is not producing any product.

Examples of potentially reasonable explanations that might result in the drugs not being deemed adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- At the beginning of an unannounced inspection, appropriate personnel are not immediately available to accurately answer the FDA investigator's questions.
- The FDA investigator arrives for an unannounced inspection, but the facility is closed due to scheduled maintenance.

V. LIMITING OF INSPECTION

An owner, operator, or agent of a drug facility who prevents an authorized representative of the FDA from conducting an inspection to the extent allowable under the law may be viewed as limiting inspection under section 501(j). Below are examples of behavior that FDA considers to constitute a limitation that may cause drugs to be adulterated under section 501(j) of the FD&C Act.

A. Limiting Access to Facilities and/or Manufacturing Processes

Preventing an authorized representative of the FDA reasonable access to an area of the site that FDA is entitled to inspect may be considered limiting the inspection. This includes the refusal to disclose or permit observation of the manufacturing processes. Examples include, but are not limited to:

- A facility orders the discontinuation of all manufacturing for the duration of the FDA inspection without a reasonable explanation.

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- A facility states that direct observation of the manufacturing process, in whole or in part, must be limited to an unreasonably short amount of time, thus preventing FDA from inspecting the facility as is usual and customary.
- A facility limits direct observation of portions of the manufacturing process without reasonable explanation.
- A facility unreasonably restricts entry to a particular portion of the facility without reasonable explanation.
- Staff at a facility causes the FDA investigator to leave the premises before the inspection is completed.

Examples of potentially reasonable explanations that might result in the drugs not being deemed adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- A facility does not provide the FDA investigator access to aseptic processing areas until the investigator accommodates the facility's documented gowning procedures.
- Training specified by the Occupational Safety and Health Administration is required before an individual may enter a particular area of the facility, and the FDA investigator has not completed such training.

B. Limiting Photography

Photographs are an integral part of an FDA inspection because they present an objective and contemporaneous representation of facility conditions. Examples of conditions or practices effectively documented by photographs include, but are not limited to: evidence of rodents or insect infestation; faulty construction or maintenance of equipment or facilities; product storage conditions; product labels and labeling; and, visible contamination of raw materials or finished products. Impeding or resisting photography by an FDA investigator may be considered a limitation if such photographs are determined by the investigator to be necessary to effectively conduct that particular inspection.

An example of a potentially reasonable explanation that might result in the drugs not being deemed adulterated under section 501(j) of the FD&C Act includes, but is not limited to:

- The chemical properties of products manufactured at the facility are such that taking photographs would adversely affect product quality.

C. Limiting Access to or Copying of Records

As explained in section III.C, the ability to access and copy records is a critical aspect of FDA inspections. Not allowing an authorized representative of the FDA access to or copying of records that FDA is entitled to inspect by law, including not providing records that FDA requests pursuant to section 704(a)(4) of the FD&C Act, may be considered limiting an inspection. Examples of records limitations include, but are not limited to:

- A facility refuses to allow the FDA investigator to review the facility's shipping records that FDA has authority to inspect.

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- A facility provides some, but not all of, the records requested by the FDA investigator that FDA has authority to inspect.
- A facility provides the FDA investigator the requested records that FDA has authority to inspect, but they are unreasonably redacted.¹¹
- A facility refuses to provide records that FDA requests pursuant to section 704(a)(4), or such records are unreasonably redacted.

D. Limiting or Preventing Collection of Samples

Collecting samples is a critical part of FDA's inspectional and regulatory activities. Section 702(a) of the FD&C Act gives FDA authority to conduct investigations and collect samples. Preventing an authorized representative of the FDA from collecting statutorily authorized samples may be considered limiting the inspection. Examples of sample limitations include, but are not limited to, declining to allow or impeding FDA to collect the following types of samples: environmental samples, finished product samples, raw material samples, in-process material samples, and reserve samples in bioequivalence and bioanalytical studies.

VI. REFUSAL TO PERMIT ENTRY OR INSPECTION

FDA interprets the term "refuses to permit entry or inspection" to include not only active, but also passive behavior and non-action by the owner, operator, or agent of a drug facility that results in an authorized representative of the FDA not being able to enter or fully inspect the facility. For purposes of this guidance, such an owner, operator, or agent shall be considered to have refused to permit entry or inspection if such owner, operator, or agent fails to take steps to permit an inspection of a factory, warehouse, or other facility. Examples include, but are not limited to:

- Without reasonable explanation, the facility bars the FDA investigator from entering the facility or certain areas of the facility by, for example, not unlocking the areas or taking other necessary actions that would permit access by the investigator.
- Following FDA's attempt to contact the facility's designated contact(s) to schedule an inspection, the facility fails to respond.
- The facility does not answer calls from the FDA investigator who is present at the facility, despite clear evidence of the presence of employees engaged in job-related functions.

¹¹ An unreasonable redaction is one that removes or obscures information that FDA is entitled to inspect. If the redaction obscures information over which FDA has no inspectional authority it generally will be considered reasonable. Section 704(a)(1) (21 U.S.C. 374(a)(1) states that FDA's inspectional authority does not extend to the following types of records: "financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualification of technical and professional personnel performing functions subject to this chapter), and research data (other than data relating to new drugs, antibiotic drugs, devices, and tobacco products and subject to reporting and inspection under regulations lawfully issued pursuant to section 355 (i) or (k) of this title, section 360i of this title, section 360j(g) of this title, or subchapter IX and data relating to other drugs, devices, or tobacco products which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 355(j) of this title)."