Guidance for Industry

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

DRAFT GUIDANCE

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Office of Regulatory Affairs (ORA)
Center for Drug Evaluation and Research (CDER)
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Center for Veterinary Medicine (CVM)
Center for Devices and Radiological Health (CDRH)

December 2022
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Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection

This Draft Guidance, when finalized will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 added section 501(j) to the Federal 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 required the Food and Drug Administration (FDA) to issue guidance that defined the circumstances that would constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection, for purposes of section 501(j).

Subsequently, on August 18, 2017, the FDA Reauthorization Act of 2017 (FDARA) (Public Law 115-52) was signed into law. Section 702(c) of FDARA amended the scope of section 501(j) of the FD&C Act to include devices. A drug or device is "deemed to be adulterated" if the owner, operator, or agent of the factory, warehouse, or establishment at which the drug or device is manufactured, processed, packed, or held delays, denies, or limits an FDA inspection or refuses to permit entry or inspection of such factory, warehouse, or establishment.

Once finalized, this draft guidance is intended to supersede the October 2014 FDA final guidance for industry entitled, "Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection." However, until this draft guidance is finalized, the October 2014 FDA guidance remains in effect until it is withdrawn and will continue to reflect FDA's current thinking on this issue.

This guidance covers facilities that are subject to inspection under section 704 of the FD&C Act.[1] This guidance defines the types of behaviors (actions, inactions, and circumstances) that FDA

[1] 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

considers to constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection for the purposes of section 501(j) of the FD&C Act.[2] 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 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."[3] 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.

In general, FDA's guidance documents 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 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.[4] An FDA inspection is a "careful, critical, official

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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).

[2] This guidance describes actions or inactions that may cause a drug or device to be adulterated under 501(j) of the FD&C Act, as amended by section 702(c) of FDARA. Actions or inactions that cause a drug or device 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 or device to be adulterated under 501(j) may nevertheless violate other provisions of the FD&C Act or other federal or state laws.

[3] FDA, Investigations Operations Manual, Section 2.2 Statutory Authority

[4] 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, [and] devices… 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, [and] devices… in interstate commerce; and… to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment or

examination of a facility to determine its compliance with the laws and regulations administered by the FDA."[5] Section 706 of FDASIA amended section 704(a) of the FD&C Act by adding 704(a)(4), which allows FDA to request, in advance of or in lieu of a drug facility inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, records or information that FDA may inspect under section 704. As it pertains to device inspections, section 704(e) requires that FDA be permitted to inspect and copy records required to be maintained under section 519 or 520(g) of the FD&C Act.

Facilities that are required to register under section 510 of the FD&C Act[6] and those that voluntarily register as outsourcing facilities under section 503B of the FD&C Act[7] are required to submit certain information to FDA. FDA uses registration information for many purposes, including scheduling of inspections. It is imperative that drug and device facilities register under section 510 of the FD&C Act when required, and that all registered facilities provide the information required by statute and FDA 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.[8]

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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, nonprescription drugs intended for human use, [and] restricted devices… 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, [and] restricted devices… 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).

[5] FDA, Investigations Operations Manual, Section 5.1.2, Inspectional Approach. 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 U.S.C. 552, 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.

[6] See also 21 C.F.R. 207, 21 C.F.R. 807. For additional information for drug establishments, see Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing. For additional information for device establishments, see https://www.fda.gov/medical-devices/device-registration-and-listing/how-register-and-list.

[7] See Guidance for Industry, Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[8] 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. Information on how to update registration and listing for device firms can be found at https://www.fda.gov/medical-devices/device-registration-and-listing/how-register-and-list#12.

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.[9] Section 501(j) of the FD&C Act, as amended by FDARA section 702(c), now deems a drug or device 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. FDA will consider reasonable explanations for behavior that may otherwise be considered to be delaying, denying, limiting, or refusing an inspection. However, where an owner, operator, or agent causes the unreasonable delay of an inspection, this may cause the drugs or devices manufactured, processed, packed, or held therein to be adulterated under section 501(j) of the FD&C Act.

A. Delay Scheduling Pre-announced Inspections

For inspections at drug facilities, 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 drug facility inspections. It is, however, FDA's 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.

For inspections at device facilities, section 704(h) of the FD&C Act, added by section 702 of FDARA, requires FDA to pre-announce inspections (other than for-cause inspections) of foreign and domestic device establishments.[10] Where pre-announcement of inspections is not required, pre-announcements may be made at FDA's discretion.

FDA's efforts to schedule pre-announced inspections may include notification via telephone or 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-workdays, and, where appropriate, scheduled manufacturing campaigns.

Examples of delay in scheduling a pre-announced inspection that may cause drugs or devices to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:

[9] Section 301 of the FD&C Act (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 of the FD&C Act (21 U.S.C 333) provides penalties for violations of section 301 of the FD&C Act.

[10] Section 702(b) of FDARA directed FDA to issue guidance that specifies how the Agency will implement processes and standards that are applicable to device inspections. See Guidance for Industry, Review and Update of Device Establishment Inspection Processes and Standards, Guidance for Industry.

- A facility will not agree to an announced 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 attempts to contact the facility's designated contact(s).

Examples of potentially reasonable explanations for scheduling delays 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:

- Manufacturing at a drug 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 applicable FDA requirements. FDA has broad authority to inspect facilities, including but not limited to the conditions and operations of a facility that bear on whether the drugs or devices are adulterated, misbranded, or are otherwise in violation of the FD&C Act. Actions by a facility's owner, operator, or agent before or during 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 inconvenience 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 or devices 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.
- 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.
- A facility agrees to the pre-announced inspection date, but when the investigator enters the facility, the necessary facility personnel are not available, or the firm's management informs the investigator that operations are shutdown, without providing a reasonable explanation.

An example of a potentially reasonable explanation that might result in the drugs or devices 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.

- A device facility does not provide FDA investigator access to environmentally controlled areas until the investigator accommodates the facility's precautionary measures to prevent contamination and risk of personal safety.

C. Delay Producing Records

A critical aspect of FDA's preparation for inspection and inspection of drug or device facilities is the review and collection of hardcopy and electronic records, files, and papers bearing on whether the drugs or devices are adulterated, misbranded, or are otherwise in violation of the FD&C Act. For example, records may be reviewed and collected to verify compliance, interstate commerce, product labeling and promotion, and to identify responsible parties. 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 or devices 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 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) or 704(e) 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 or devices 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, accessing the records would unnecessarily disrupt the operation, and the records are provided as soon as practicable.
- The volume of the records requested is sufficiently large as to require reasonable additional time to compile.
- The records requested are stored off-site and require reasonable additional time to collect.

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 that is agreed upon by the facility and FDA.

IV. DENIAL OF INSPECTION

FDA interprets the word "deny" to include any behavior by the owner, operator, or agent of a drug or device facility to prevent an authorized representative of 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 or devices 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 or devices.
- 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 or devices 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 or device facility who prevents an authorized representative of FDA from conducting an inspection to the extent allowable under the law may be viewed as limiting inspection under section 501(j) of the FD&C Act. Below are examples of behavior that FDA considers to constitute a limitation that may cause drugs or devices 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 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.
- The firm interrupts production activities to prevent FDA investigators from observing production operations.
- A facility limits FDA's direct observation of the manufacturing process, in whole or in part, 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, without reasonable explanation.

Examples of potentially reasonable explanations that might result in the drugs or devices 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 components, containers, closures, or 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 or devices 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.
- The facility can document that taking photographs of any raw material or assembly 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 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) or 704(e) of the FD&C Act, may be considered limiting an inspection. Examples of limiting access to records 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.
- A facility provides some, but not all, 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 704(e), or such records are unreasonably redacted.
- A facility maintains electronic records but omits or limits the data contained in the electronic records when providing electronic copies of the records to FDA. This includes but is not limited to actions such as removing data columns in Excel, removing data from the electronic record when providing the record to FDA, exporting data into reports without including all of the data fields (unless otherwise requested by FDA), or locking the electronic worksheet so that the data cannot be searched, sorted, or analyzed by FDA.
- A facility identifies an electronic record as the original but does not provide an electronic copy of that record (or data query) to FDA pursuant to FDA's request.

D. Limiting or Preventing Collection of Samples

Collecting samples is a critical part of FDA's inspectional and regulatory activities. Section 702 of the FD&C Act gives FDA authority to conduct investigations and collect samples. Preventing an authorized representative of 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 from collecting the following types of samples: environmental samples, finished product samples, raw material samples, in-process material samples, reserve samples in bioequivalence and bioanalytical studies, and labeling.

VI. REFUSAL TO PERMIT ENTRY OR INSPECTION

[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) of the FD&C Act (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 qualifications of technical and professional personnel performing functions subject to this Act), 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 505(i) or (k), section 519, section 520(g), or chapter 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 505(j))."

FDA interprets the term "refuses to permit entry or inspection" to include not only active, but also passive behavior and inaction by the owner, operator, or agent of a facility that results in an authorized representative of 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 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, despite clear evidence of the presence of employees engaged in job-related functions.