Guidance for Industry

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

DRAFT GUIDANCE

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For questions regarding this draft document contact Office of Regulatory Affairs, Office of Policy and Risk Management at FDASIAImplementationORA@fda.hhs.gov.

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)

July 12, 2013

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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), not later than one year after the date of enactment of FDASIA, 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 This draft guidance defines the types of actions, inaction, and circumstances that the FDA considers to constitute delaying, denying, or limiting inspection, or refusing to permit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).[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).

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

[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] 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.

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 appointed employees of the FDA or designated officers to enter, at reasonable times, and inspect, at reasonable times and within reasonable limits and in a reasonable manner, facilities under the jurisdiction of the FD&C Act.[3] 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. Section 706 of FDASIA amended section 704(a) of the FD&C Act by allowing FDA to request, in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, any records or information that FDA may inspect under section 704(a).

The FD&C Act makes refusing to permit entry or inspection and refusing to permit access to or copying of any record as required by section 704(a) prohibited acts,[4] subjecting any person responsible for such refusals to criminal penalties under section 303. 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 drug to be adulterated under section 501(j) of the FD&C Act.

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[3] 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 an FDA 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).

[4] 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."

A. Delay Scheduling Pre-announced Inspections

While not required by the FD&C Act, FDA may (and often does) contact a facility's management in advance and pre-announce an inspection. This pre-announcement is intended to facilitate the inspection process and ensure that appropriate records and personnel will be made available. Generally, for drug products, pre-approval and pre-license inspections, and most inspections of foreign facilities are scheduled before an investigator arrives at the inspection site.

FDA efforts to schedule pre-announced inspections include sending correspondence to the facility's management, including the facility's U.S. agent, if the facility is a foreign facility. FDA's goal is to contact facilities within a reasonable time prior to the proposed start date of the inspection. FDA will make reasonable accommodations for local conditions, such as weather or security situations, holidays, and other non-work days, and 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).

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.
- 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.

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 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 records FDA has authority to inspect within a specific, reasonable timeframe, but the facility fails to produce the requested records within the timeframe requested by FDA, without adequate justification.
- 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 adequate justification.

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 or deceive 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 an inspection.
- A facility does not allow the FDA investigator to begin an inspection of a facility, even if it has been pre-scheduled.
- A facility does not allow the FDA investigator to inspect the facility because certain staff members are not present.
- A facility does not allow the FDA investigator to inspect the facility by falsely alleging the facility does not manufacture drugs.

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 under the law may be considered limiting the inspection. This includes the denial 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.
- 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.
- A facility unreasonably restricts entry to a particular facility without adequate justification.
- Staff at a facility cause the FDA investigator to leave the premises before the inspection is completed.

B. Limiting Photography

Photographs are an integral part of an FDA inspection because they present an accurate picture of facility conditions. Not allowing photography by an FDA investigator may be considered a limitation if such photographs are determined by the investigator(s) to be necessary to effectively conduct that particular inspection. 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.

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.
- 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 the records are unreasonably redacted.[5]

[5] An unreasonable redaction is one that removes or obscures information that FDA is entitled to inspect by law. If the redaction does not obscure information over which FDA has no inspectional authority it generally will be considered reasonable. Section 704 (21 U.S.C. 374) states that FDA's inspectional authority does not extend to the

- 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 samples allowable under the law may be considered limiting the inspection. Examples of sample limitations include, but are not limited to, declining to allow 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 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 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 does not take steps to permit an inspection of a factory, warehouse, or other facility. Examples include, but are not limited to:

- The facility bars the FDA investigator from entering the facility or certain areas of the facility, for example, by not unlocking the areas or taking other necessary actions that would permit access by the investigator(s).
- Following FDA's attempt to contact the facility's designated contact(s), 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.

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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)."