PDA Parenteral Drug Association
India Chapter

The Quality Edifice and Sterility Assurance of Parenterals

Nov 11-12, 2013 Mumbai

Connecting People, Science and Regulation

Sessions:

PDA Parenteral Drug Association
India Chapter

1. Investigations- The ABC of expectations
2. Environmental Monitoring- Need for preventive controls & verification possibilities
3. Understanding Risks for predictive controls
4. Uncovering nuances of FDA's draft guidance on 'Circumstances that Constitute Delaying, Denying ,Limiting ,Or Refusing a Drug Inspection.
5. Manual Aseptic Processing- The Crossroads
6. Sterility Assurance Packages- Essentials and Expectations

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Case 4

Uncovering nuances of FDA's draft guidance on 'Circumstances that Constitute Delaying, Denying, Limiting Or Refusing a Drug Inspection'.

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Uncovering nuances of FDA's draft guidance on Circumstances that Constitute Delaying, Denying Limiting or Refusing a Drug Inspection

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Insides

Introduction

- The Guidance document illustrates circumstances where the FDA will treat the occurrence as contrary to section 501(j).
- These are divided into four sections:

(1) Delay of Inspection

(2) Denial of Inspection

(3) Limiting of Inspection

(4) Refusal to Permit Entry.

Introduction

Defines types of actions, inactions and circumstances that FDA considers to constitute Delay, Denying, Limiting or Refusing

Background

- In the past, some firms have sought to refuse or delay entry of FDA inspectors into their facility, hoping the additional time could be used to either clean up a facility or expunge certain records.
- Section 704(a) of the FD&C Act provides FDA authority for inspection
  - -At reasonable times
  - -Within reasonable limits
  - -In a reasonable manner

Background

- Section 706 of FDASIA amended section 704(a) of the FD&C act allowing FDA to request in advance of or in lieu of an inspection
- Now Section 707 of the act - the statute that covers the definition of adulterated drugs – to include the products of any establishment that delays, denies or limits an inspection, or refuses to permit entry or inspection.

Background

- Section 707 of FDASIA, which added 501(j) to the FD&C Act, the FDA now deems as **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**". (color & emphasis added)

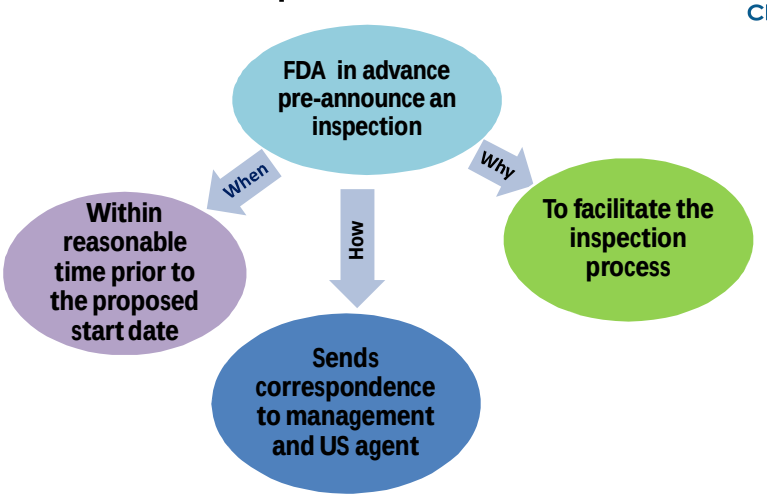
Background

- FDA immediately makes one important caveat: "FDA does not interpret the four terms describing prohibited behavior necessarily to be mutually exclusive"
- Meaning that companies may find their product adulterated under the statute in more than one way depending on their behavior.

Delay of Inspections

- A – Delay scheduling Pre-announced Inspections
- B – Delay during an Inspection
- C – Delay Producing Records

Delay scheduling Pre-announced Inspections



Delay scheduling Pre-announced Inspections - Examples

Drugs to be adulterated under section 501 (j) of the FD&C act - when

A facility does not agree to a proposed inspection start date without giving a reasonable explanation for its failure to do so	Requesting a reschedule of inspection without giving a reasonable explanation	Facility does not respond when FDA is attempting to contact

Delay during an inspection

FDA Inspection

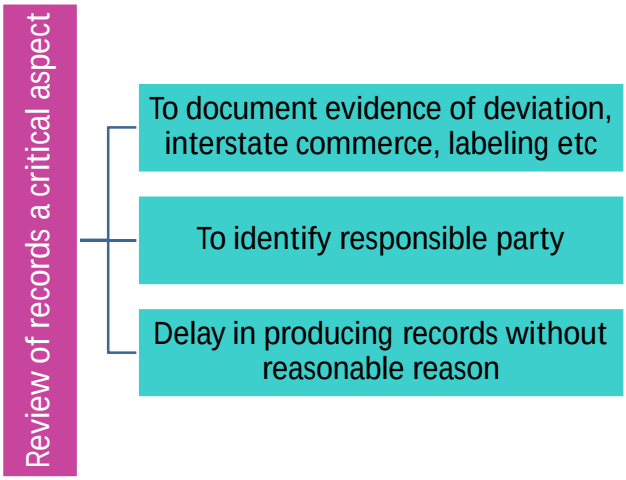
- Intended to enable review facility's compliance
- Authority to inspect things that bear compliance / non compliance
- **Aware that it may cause minor confusion / inconvenience Minor delays by the facility generally would not be considered unreasonable**

Delay during an inspection - Examples

Before or after beginning of an inspection- actions that impede FDA investigator from performing the inspection in a reasonable manner may be considered delaying an inspection

Facility does not allow access to an area until a specific future date or time even though the area is operational and is an area of inspection site	Facility leaves the investigator in a conference room without access to necessary documentation or responsible individuals for an unreasonable time

Delay producing records



Delay producing records - Examples

Drugs to be adulterated under section 501 (j) of the FD&C act - when

During an inspection, the FDA investigator requests records to inspect within a specific timeframe, but the facility fails to produce the requested records without adequate justification

Delay of Inspections – Case studies

- Facility has agreed to other regulatory inspection and it is already scheduled
- Facility is under shut down and under modification
- Change in management, organizational restructuring

Delay of Inspections – Case studies

- The investigator identifies the presence of torn raw data records in the waste area and asks the one of the staff member to remove for investigator's review.
- The staff member consults his supervisor and changes the torn records and presents it to the investigator.
- The FDA investigator was directed away from the requested documents and this forced them to having to locate and reassemble the torn records

Denial of Inspection

- The word Deny is interpreted
- As a behavior to prevent from conducting an inspection

or

- To prevent completing an inspection

Behavior includes statements or physical actions intended to avoid, mislead or deceive the investigator

Denial of Inspection

Behavior that may constitute a denial

Not allowing to inspect by falsely alleging the facility does not manufacture drugs	Not allowing the investigator to begin a pre-scheduled inspection	Not allowing to inspect the facility because some staff members are not present

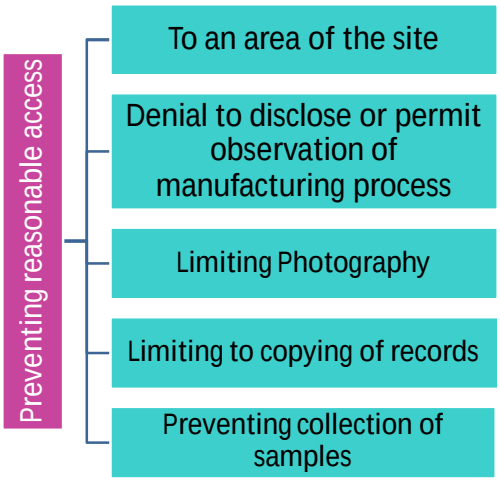
Denial of Inspection – Case studies

- The investigator was denied access to the process area since the firm had a policy of allowing only authorized and qualified people and also there was no provision for anyone to observe the process from a glass panel or an outer corridor.

Limiting of Inspection

- A – Limiting access to facilities and / or manufacturing process
- B – Limiting Photography
- C – Limiting access to or copying of records
- D – Limiting or preventing collection of samples

Limiting of Inspection



Limiting access to facilities and / or manufacturing process - Examples

Drugs to be adulterated under section 501 (j) of the FD&C act - when

Facility orders discontinuation of manufacturing for the duration of inspection without reasonable explanation	Facility states direct observation of manufacturing process to an unreasonably short amount of time	Staff at a facility cause the FDA investigator to leave the premises before inspection is completed	Restricts entry to a particular facility without adequate justification

Limiting Photography - Examples

Drugs to be adulterated under section 501 (j) of the FD&C act - when

Conditions or practices as evidence of
rodents or insect infestations
Faulty construction or maintenance or equipment or facilities
Product storage conditions
product labels and labeling
visible contamination of raw material and finished products

Limiting Access to or Copying of Records - Examples

Drugs to be adulterated under section 501 (j) of the FD&C act - when

Facility refuses to allow to review the facility's shipping records	Facility provides some, but not all of the records requested	The records are unreasonably redacted

Limiting or preventing collection of samples - Examples

Drugs to be adulterated under section 501 (j) of the FD&C act - when

Declining to allow to collect samples of environmental monitoring

Finished product , raw material, in-process and reserve samples

Limiting of Inspection – Case studies

- The investigator finds unlabeled cartons and vials in the stability chambers and there were no entries made for such samples in the log book. The investigator requests the staff member to remove it for investigators review.
- The staff member states that these cartons and vials were for some experimental studies and does not come under the scope of the inspection.

Limiting of Inspection – Case studies

- An aseptic filling line was in use and the area was operational and was an area of the inspection site that FDA has authority to inspect. The investigator was obstructed from performing an inspection stating that the product was not in the audit purview.
- The investigator later finds that the aseptic filling line was used for products for the US market.

Refusal to permit entry or inspection

- The word Refusal is interpreted
- To include passive behavior and non – action that results in an investigator not being able to enter or inspect the facility

Refusal to permit entry or inspection - Examples

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Drugs to be adulterated under section 501 (j) of the FD&C act - when

Facility bars the FDA from entering the facility or certain areas by not unlocking the areas or taking other necessary actions that would permit access	Upon FDA's attempt to contact the facility's designated personnel – facility fails to respond	Facility does not answer calls

Refusal to permit entry or inspection – Case studies

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- QA personnel provided the FDA investigator misleading information related to the failure investigation report of the aseptic process simulation.
- The QA personnel denied several times that the firm had performed trial media fill runs where as the same were traced in the QC logs.
- In addition, QA personnel refused to provide requested information regarding detailed observation of samples of the same trial media fill runs

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THANK YOU FOR YOUR ENGAGEMENT!

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