FDA/State Collaboration and Communication: How FDA Can Support State Actions

Inter-governmental Working Meeting on Drug Compounding
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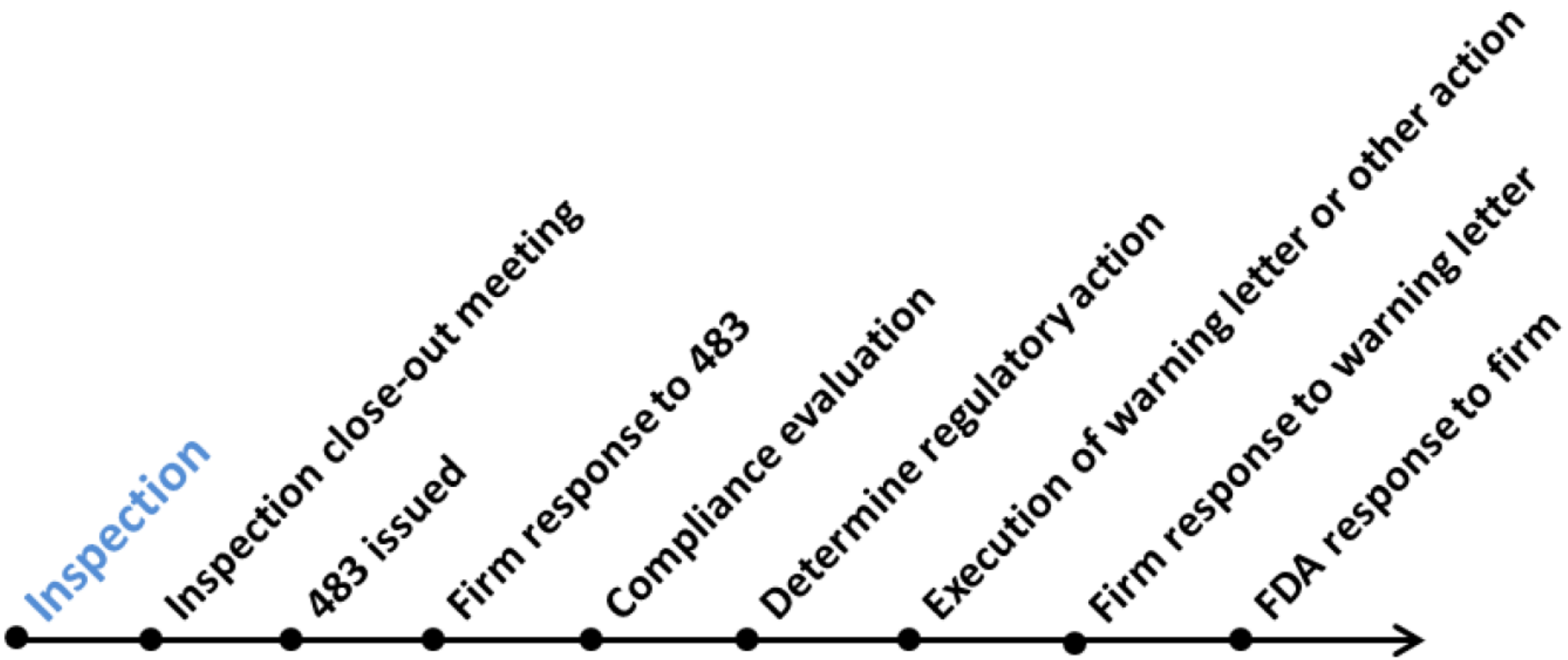
Overview

- FDA process from inspection to regulatory letter reply
- Descriptions of
  - Forms FDA 483
  - Warning Letters
  - Untitled Letters
- FDA and State Enforcement Tools Often Complement and Supplement Each Other
- How FDA can support state actions

FDA Process from Inspection to Regulatory Letter Reply



Forms FDA 483

- Issued to management at the conclusion of an inspection when FDA investigators have observed conditions that in their judgment may constitute violations of the FD&C Act and FDA regulations
- Does not constitute a final Agency determination as to whether any condition is in violation of the FD&C Act or FDA regulations
- Posted with appropriate redactions on FDA's compounding website following the conclusion of the inspection

Warning Letters

- Because a Warning Letter is informal and advisory and does not commit FDA to take enforcement action, FDA does not consider a Warning Letter to be final agency action.
- Warning Letters are issued for violations of regulatory significance, to achieve voluntary compliance and to establish prior notice.
- Warning Letters issued to compounders often describe failures to meet the conditions of Sections 503A and 503B, violations of the prohibition on insanitary conditions, CGMP requirements, and other applicable requirements in federal law.
- FDA posts Warning Letters issued to compounders, with appropriate redactions, on its compounding website.

Untitled Letters

- Similar to a Warning Letter, FDA does not consider an Untitled Letter to be final agency action.
- An Untitled Letter cites violations that do not meet the threshold of regulatory significance for a Warning Letter.
- Unlike a Warning Letter, an Untitled Letter does not include a warning statement that failure to promptly correct a violation may result in an enforcement action, and it does not evoke a mandated follow-up inspection.

FDA and State Enforcement Tools Often Complement and Supplement Each Other

- FDA's primary civil enforcement tools against compounders and compounded drugs are injunctions and seizures.
- FDA may recommend or request, but not require, recalls of compounded drugs.
- States often have the ability to use different tools and act more rapidly than FDA to stop unsafe activity when identified, such as through immediate state licensure suspension.
- FDA greatly values state enforcement actions and encourages states to seek FDA's support in their enforcement actions where such support would be helpful.

How FDA can support state actions

- Request that states join FDA on compounding inspections
- Provide factual witness testimony
- Provide copies of unredacted or partially redacted
  - Establishment Inspection Reports (EIRs)
  - Forms FDA 483
  - Warning Letters and Untitled Letters
- Proactively share information with states
- Discuss with states the significance of the observations in Forms FDA 483 and the violations in warning and untitled letters and the actions, if any, FDA is considering taking to address them

How FDA can support state actions

Request that states join FDA on compounding inspections

- FDA values state participation in inspections
- Joint inspections allow states to directly observe the compounder's facility and operations, which may be useful to support later enforcement actions where needed
- Joint inspections support greater oversight collaboration between FDA and states

How FDA can support state actions

Provide FDA factual witness testimony

- FDA can provide its investigators as witnesses to give factual testimony about observations made during inspections
- The testimony can be provided as a written declaration or affidavit or as verbal testimony at a state hearing
- Requests for FDA factual witnesses should be made to Lauren DiPaola with FDA's Office of Policy and Risk Management. Lauren.Dipaola@fda.hhs.gov

How FDA can support state actions

Provide copies of unredacted or partially redacted EIRs, Forms FDA 483s, Warning Letters and Untitled Letters

- The amount and type of information that FDA may disclose to the requesting state officials may depend on whether they are commissioned officials or have entered into a 21 CFR 20.88 agreement with FDA.
  - Commissioned officials may receive unredacted versions of documents
  - Officials under 20.88 agreements may receive versions of these documents with trade secret information redacted

How FDA can support state actions

Proactively share information with states

- FDA currently proactively shares information where possible with states about complaints, voluntary recalls or other issues related to compounding facilities.
  - The amount and type of information that FDA may proactively share may depend on whether state officials are commissioned officials or have entered into a 21 CFR 20.88 agreement with FDA.
- In addition, FDA is planning to proactively share with states:
  - Warning letters and FDA Form 483s issued to compounding facilities with nonpublic information redacted
  - Information about compounding facilities that resume operations after voluntarily ceasing operations (Action Item 4)

How FDA can support state actions

Discuss with states the significance of the observations in Forms FDA 483 and violations in warning and untitled letters and the actions, if any, FDA is considering taking to address them

- As with the documents themselves, the amount and type of information that FDA may disclose to the requesting state officials may depend on whether they are commissioned officials or have entered into a 21 CFR 20.88 agreement with FDA.
- Note that observations in Forms FDA 483 should be listed in order of significance.

How FDA can support state actions

Examples of significant observations in a Form FDA 483 are:

- Direct evidence of contamination
- Poor aseptic practices that pose a serious contamination hazard
- Excessive beyond use dates without supportive data
- Fundamental facility or process control flaws that pose a serious contamination hazard (e.g., sterile product manipulated in an area that is not ISO 5, infrequent or no disinfection of materials/supplies before placement in ISO 5 critical area, equipment not sterilized)
- Significant sterility test or media fill failures
- Excessive in-process hold times that seriously increase bioburden or endotoxin risk