Presentation to Parenteral Drug Association

Responding to FDA 483s and Warning Letters

Date: 2006 May 17
Introduction

Main points of discussion:

- Brief Historical Overview
- Form FDA 483
- Responding to the FDA 483
- Warning Letter
- Responding to a Warning Letter
- Common Mistakes
Historical Overview

- Form FDA 483 created in 1953 by addition of Section 704(b) to FD&C Act
- Intended to eliminate possibility of FDA action against a firm without prior notice
- Notice of Inspection (Form FDA 482) was also mandated
- Current Warning Letter developed from the Notice of Adverse Findings and the Regulatory Letter
- Warning Letters may require Center concurrence or may be issued directly by a District Office
Form FDA 483

- Provided to assist firms in complying with Acts enforced by FDA
- List of objectionable conditions and practices which indicate violations
- Presented at the conclusion of an inspection (close-out)
- Close-out provides opportunity for clarification & final review (releasable under the FOIA)
FDA’s view of the 483:

- Specific feedback on actual industry practice to assist in voluntary compliance
- Means for FDA to comply with the requirement of Section 704(b)
- Establishes a background of prior warning notwithstanding requirement of strict liability
Industry’s view of the 483:

- Availability under FOIA (see 21 CFR 20.101(a)) provides “public scorecard”
- Represents list of GMP concerns (albeit in the “judgment” of one or more investigators)
- Currency of cGMPs is maintained and advanced through issuance of 483s
Verbal Response

- At close-out, prior to issuance, is the opportunity to clarify misunderstandings

- Deficiencies corrected during inspection can and should be pointed out

- Not a substitute for a full written response
Responding to the FDA 483

Written Response

- Respond quickly (10 to 15 days), even if the initial response will be preliminary
- Understand significance of observations relating to product quality
- Acknowledge observations and describe corrections being made
- Immediate corrections if possible, otherwise set realistic time frames
Responding to the FDA 483

Written Response (continued)

- Provide assurance when possible that quality of distributed product (public safety) is not a concern

- Address all deficiencies; provide plan of action with target dates; always expect FDA follow-up

- Emphasize that “global” or “systemic” issues have been addressed
Example of a Good Response

Inspectional Observation

- Instruments 12, 16, and 382, which were in use during the manufacture of Lots 5, 6, and 7 of Product X had exceeded due dates for their next scheduled calibrations

- GMP requirement: 21 CFR 211.68(a)
Example of a Good Response

Elements of Successful Written Response:

- Instruments were calibrated and found to be within limits (records attached)
- Usage in manufacture of Product X has no effect on quality
- Calibration program to be reviewed to assure no other such instances
- Review of program along with any needed corrections will be completed in 60 days; documentation will be submitted
Example of a Good Response

Key Features of Each Element

- Immediate corrections made when possible and adequately documented
- Effect of deviation on product quality is objectively assessed
- Systemic and/or global ramifications of observation are addressed
- Target date set for ongoing actions, with promise to submit documentation
Warning Letters

- Considered an *advisory* action
- Intended to elicit voluntary correction
- Establishes background of prior warning
- Should only be issued for violations of “regulatory significance”
- Published under FOI immediately
Warning Letters

- Violations specified in a Warning Letter represent concerns not only of an investigator, but of District and/or Center compliance officers.

- Possible repercussions: recall, seizure, injunction, monetary fine, debarment, disqualification, license suspension or revocation, prosecution, denial of access to U.S. market (e.g., foreign API suppliers).
Responding to a Warning Letter

- Notify top management of the scope of the problem (see 21 CFR 211.180(f) also)
- Contact the District Director or Compliance Officer
- Provide written response
  - Acknowledge obligation to comply with law
  - Discuss impact on product quality
  - Global and/or systemic corrections
  - Corrective actions and timetable for completion
Request Meeting with FDA

Key aspects of meeting:

● Ensure common understanding of GMP concerns

● Verify adequacy of proposed corrections

● Reveal if further action by FDA is planned

● Achieve agreement on how to proceed

● Provide a written summary, including any clarifications and additional commitments

● Provide periodic updates of progress
First choice is to work with companies informally* to identify and correct problems

Second choice is to use regulatory tools

In some cases the second choice comes first by requirement or default

* Warning Letters are “advisory” actions (Chapter 4, RPM)

† Source: Steven Gutman, Director, OIVD, CDRH

www.fda.gov/cdrh/oivd/presentations.html
Avoiding Enforcement Actions

- Only proven technique: establishing an effective Quality System

- Key organizational attributes: communication and accountability

- Establish entails *defining, documenting* (in writing or electronically), and *implementing*
# Enforcement Statistics

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GMP Inspections — Key References

- 21 CFR Parts 210, 211, et al.
- Compliance Programs (CPGM)
- Inspectional Guidance, ITGs, ITM
- Mandatory Recordkeeping May 16, 2002 (67 FR 34939) — pharmaceuticals
- Court decisions, e.g. U.S. v Barr Laboratories
- FDA website (www.fda.gov). “Search FDA Site”
GMP Inspections — Key References (cont.)

- Warning Letters
- EIRs and 483s releasable under FOIA
- CDER and CBER (the respective Divisions of Manufacturing and Product Quality)
- Guidance Documents
- Compliance Policy Guides
- IOM, RPM, Field Management Directives (FMD)
- China Training Program (FDA / ISPE / Peking Univ)
2005 FDA cGMP China Training Program
December 5-7, Beijing, China

The U.S. Food and Drug Administration, Peking University, and ISPE are co-sponsoring a training program to provide the latest updates from the FDA on current regulations and guidances, and interactive training workshops on oral solid dosage, and API manufacturing.

- Federal Register Notice (TXF) [PDF]
- Program Information [PDF]
- For registration information, please contact Mark Stefko at ISPE, (813) 739-2287
- Presentations (12/14/2005)
  - FDA Overview [PowerPoint]
  - Solid Oral Dosage Forms, [PowerPoint] Nicholas Bulay, CDER
  - cGMP in the USA, [PowerPoint] Nicholas Bulay, CDER
  - Counterfeit Drugs, [PowerPoint] Nicholas Bulay, CDER
  - FDA cGMP Inspections, [PowerPoint] Robert C. Horan, Ph.D., CDER
  - FDA API Inspections, [PowerPoint] Robert C. Horan, Ph.D., CDER
  - The FDA Process for Approving Generic Drugs [PowerPoint]
Avoiding Unnecessary Problems

- DON’T set unrealistic goals
- DON’T blame everything on a lack of training
- DON’T trivialize product complaints
- DON’T fail to proofread correspondence
- DON’T cite other firms’ practices
- DON’T fail to implement promised corrections
Summary

- Compliance is the ultimate objective
- Protection of public health *through compliance with laws and regulations* should be a mutual objective
- Compliance can require a significant financial commitment
- Effective communication is vital
- Accountability must be achieved
Thank you

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