Presentation to Parenteral Drug Association

Responding to FDA 483s and Warning Letters

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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

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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)

Form FDA 483 (cont.)

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***

Form FDA 483 (cont.)

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**

Responding to the FDA 483

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

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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

Compliance (Enforcement)†

- 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

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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***

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Enforcement Statistics

	FY 04	FY 03	FY 02	FY 01	FY 00	FY 99
Conviction	196	206	271	360	353	211
Injunction	13	22	15	12	9	8
Recall	4,670	4,627	5,025	4,563	3,716	3,736
Seizure	10	25	13	27	36	25
Warning Letter	737	545	755	1,032	1,154	900

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"

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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)

GMP Inspections — Key References (cont.)

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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

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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**

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Thank you

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