ARNOLD & PORTER LLP

2002 PDA/FDA JOINT REGULATORY CONFERENCE

From 483 to Warning Letter to Consent Decree:

Can You Avoid Escalation of FDA Actions?

Washington DC

September 2002

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Introduction

- Perspective of someone counseling drug and device firms for 23 years
- Usually called in after 483 or Warning Letter
- Events often set in stone during inspection
  - Cannot change what FDA saw and heard
  - Ugly confrontations can lead to criminal prosecutions, even when compliance was not seriously in doubt

FDA Has Incentives to Avoid Escalation

- Warning Letters have internal cost at FDA
  - Now undergoing multiple layers of review
- Consent Decrees are even more costly
  - 1 FTE per CD to monitor
  - Voluminous filings to be read and checked
  - Multiple inspections possible

STRATEGIC GOAL:
Convince FDA Escalation Is Not Necessary

- FDA wants quality in drug products
  - Has limited ability to test, to inspect, to design
- FDA wants self-regulation
  - Increasing stress on CAPA and QSIT approaches
- FDA wants compliance, not disgorgement

Analyzing the 483: STEP 1

- What is FDA telling the company?
  - Reduce the 483 to bullets 1-5 words long
    - "No SOPs"
    - "Fail to follow SOPs"
    - "Lack documented training"
    - "Poor records"
    - "Failure to monitor compliance"
    - "Failure to investigate/solve problems"

Analyzing the 483: STEP 2

- Why did FDA reach this conclusion?
  - What did FDA see, hear, read?
  - Has FDA observed this issue before?
    - At this site
    - Elsewhere in the company
  - Did FDA raise the issue before?
    - FDA does not like repeat offenses

Analyzing the 483: STEP 3

- Is FDA clearly wrong?
  - Different question from "Is FDA right?"
    - Easier way to approach self-criticism and candor
  - Management judgment, not line opinion
    - People responsible for compliance may not see things so clearly
    - Leadership tension: defend team, but avoid losing fight with FDA
  - Influences total approach to response
    - Culture, people, scope of remediation

Responding to the 483: STEP 1

- Address the major themes of FDA observation
  - Focus on the bullets you identified
  - Individual actions must show sensitivity to theme
- Fight FDA — but only if FDA is clearly wrong
  - Very rare but it happens
  - Litigation vs. FDA is very tough
  - Pick your fights carefully and be sure you are right

Responding to the 483: STEP 2

- Remediate any problems systemically
  - Do not limit vision to narrow 483 observation or to single site
- Make sure remediation plan is feasible, timely, and supported by management
  - Promises that are impossible or facially silly won't convince FDA
  - Resources and priorities must be maintained

Responding to the 483: STEP 3

- Show FDA that the company "gets it"
  - Recognizes thematic issues
  - Has a commitment to remediate
  - Describes the remediation plan in sufficient detail to persuade FDA it is real
- Promise to keep (and keep) FDA informed of action on plan
  - Manage FDA's expectations throughout remediation

Responding to the 483: STEP 4

- Should you meet with FDA?
  - Why?
  - What will you say?
  - When?
- FDA will still look for the written communications
  - The writing, not the handshakes, govern

Getting a Warning Letter

- Interpreting the Letter
  - Is FDA dissatisfied with the 483 Response?
  - You need to read carefully and perhaps meet with District Office or higher
  - Don't ask FDA for advice; tell FDA your plans and seek reaction
- FDA may simply be creating a written record, or more seriously warning that the company "does not get it"

Responding to the Warning Letter

- If FDA is not dissatisfied with the 483 response, proceed with the plan submitted
- Written response to Warning Letter should reaffirm commitment to plan
- Understand that failures or delays may have more severe risks attached

Responding to the Warning Letter

- If FDA is dissatisfied with the 483 response, identify and address the source(s) of the problem(s)
- Written response needs to provide a new plan
- This plan is the “last chance” to avoid escalation of regulatory reaction from FDA

Warning Letter Publicity

- Warning Letters are public; you need to consider affected parties
  - Investors & investment analysts
  - Employees
  - Licensors, licensees, & co-marketers; vendors
  - Health care providers
  - Patients

Warning Letter Publicity and FDA

- FDA will read your PR materials
- Do not put FDA into an awkward or defensive position
- Do not put words in FDA's mouth

QUESTIONS AND DISCUSSION

(The floor is open)

If you have additional questions, feel free to contact me at:

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