ARNOLD & PORTER

PHARMACEUTICAL REGULATORY AND COMPLIANCE CONGRESS AND BEST PRACTICES FORUM

MANUFACTURING AND GMP ISSUES: PREPARING FOR AN FDA INSPECTION

ARTHUR N. LEVINE
ARNOLD & PORTER
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CONSEQUENCES OF POOR GMP INSPECTIONS

- Voluntary product recalls, alerts, temporary cessation of manufacture or distribution
- Increased FDA oversight
  - re-inspection
  - inspection of other sites
  - heightened attention to ADEs and other reports
- FDA regulatory action
  - Significant inspectional observations
  - Warning letter
  - "Compliance hold" on pending NDAs and supplements, and exports
  - Disruption of clinical research
  - Withdrawal of NDA
  - Seizure, injunction, criminal prosecution

ADDITIONAL IMPACTS

- Revised processes and procedures
- Adverse government contract decisions
- Disruption of contractual obligations
- Reassessment by the business/investment community
- Strains on employee morale
- Adverse publicity
- Increased product liability exposure
- Shareholder suits
- False Claims Act suits (implied certification)

THE REASONS FOR POOR GMP INSPECTIONS

- Inadequate QA
  - QA authority and resources
  - Training
  - Supervision
  - SOPs and document control
  - Shared understanding of quality objectives
  - Performance
  - Financial support
- Inadequate management controls over operations and quality
  - Establishing the corporate compliance culture
  - Communicating the corporate compliance culture
  - Enforcing accountability
  - Clearly identified responsibility

- Ineffective auditing and monitoring
- Unclear or inadequate documentation/inadequate change control
- Poor validation
- Failure to recognize indicators of manufacturing or quality system problems
- Weak mechanisms of preventive and corrective action
- Unresolved cGMP deficiencies (“repeat violations”)
- Inadequate preparation for FDA inspection

FDA GMP Inspections

- Bottom-up inspections
  - recalls/alerts
  - OOS findings
  - OOS/manufacturing error investigations and reports
  - QA release decisions
  - QA/manufacturing changes
  - environmental excursions
  - CAPA
- Top-Down Inspections
  - management controls
  - quality reports and reviews
  - quality unit authority/quality system infrastructure
  - quality manual/documentation
  - training processes
  - validation/process control system

FDA GMP INSPECTION REALITIES

- Demonstrating a "state of control"
- Your GMP compliance is what it is
- Performance often lags behind system controls
- Documents speak for themselves

- Exercising good communication
- Being responsive to investigator requests
- Daily meetings/daily reports
- Avoiding 483 surprises

FDA GMP INSPECTION ISSUES

- Perceived failure to fully correct previous observations or fully meet prior commitments
- Perceived lack of candor
- Perceived lack of compliance with SOPs
- Perceived superficial or inadequate quality operations (*e.g.*, failure to identify and resolve root causes)
- Perceived lack of alignment between manufacturing/shipment decisions and quality data
- Perceived lack of understanding of quality processes
- Investigator expectations exceeding cGMP

MORE QUESTIONS?

ARTHUR N. LEVINE
Arthur_Levine@aporter.com
(202) 942-5740