Current Good Manufacturing Practices, and FDA Enforcement Actions and Inspections

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Current Good Manufacturing Practices (cGMPs)

- 21 C.F.R. Parts 210 and 211
- Apply to the manufacture, processing, packing, or holding of a drug
- Products not produced or packaged in compliance with FDA cGMP regulations are legally adulterated
- Manufacturers must proactively ensure drug safety, purity, and effectiveness

Failure to comply with cGMPs can result in an FDA enforcement action:

- FDA Warning Letter
- FDA seizure of products
- Civil (court) injunction prohibiting some or all further sales, and/or recalling product already on the market
- Possible decree imposing substantial fines

Failure to comply with cGMPs can result in an FDA enforcement action

- Preclusion of government contracts
- Import alerts
- Criminal liability for the company and individual employees

FDA Warning Letters

- A warning letter will specify the cGMP violations and demand to know how the problem will be corrected.
- Failure to respond may lead to more severe enforcement actions by the FDA.

Seizure

- A court action is brought by FDA to remove a product from interstate commerce because it is in violation of the law. (21 U.S.C. § 334)

Seizure: the example of PerkinElmer

- In February 2004 FDA seized PerkinElmer neonatal screening kits for failure to follow cGMPs
- Observations from prior FDA inspections were not addressed; company was seen as nonresponsive to sustained prodding
- The seizure caused threat of a public health crisis due to risk of exhausting neonatal screening test supplies nationwide

Seizure: the example of Local Repack

- In 2003, FDA seized all drugs bearing foreign labels or labeled as repacked by Local Repack and/or Alliance Wholesale Distributors
- Was the result of alleged repeated failure to comply with cGMPs, including misbranding and questionable handling and storage of products

Lessons from Local Repack

- **Do** record lot numbers;
- **Don’t** leave labels lying around;
- **Don’t** leave empty containers and boxes of drugs lying around; and
- **Don’t** claim quality control employee signed off on repackaging records on his days off.

Injunction for cGMP violations

- A civil action taken against an individual and/or firm to stop production or distribution of a product manufactured or sold in violation of applicable law and regulations. (21 U.S.C. § 332)
- The government does not generally have to prove irreparable harm when the statute authorizes injunctive relief.
- Generally, need only prove a violation of the statute.

Injunction for cGMP violations

- Possible shut down order: Company must fix manufacturing problems before FDA will allow sales to continue
- Can cause products to be in short supply
- Can cause delay in release of new products and recalls of older ones
- Designation of independent auditor

Injunction for GMP violations

- *U.S. v. Barr Labs*
  - FDA, the "humorless warden" faced off against Barr Labs, the "uncooperative prisoner"
  - Court prohibited further product distribution until Barr completed studies validating product identity and safety
  - Court ordered Barr to recall released drugs

Injunction for GMP violations

- *U.S. v. Andersen Products, Inc.*
  - Company used unvalidated sterilizing system
  - But FDA had not promulgated an industry standard
  - Court refused to impose injunction
  - Injunction is not appropriate when there is no evidence that the company will violate the cGMP regulations in the future

Consent decrees – Abbott Labs

- In 1999 Abbott Labs paid $100 million to settle alleged quality systems violations for devices
- Amount was equal to anticipated profits from continuing sale of product
- Allowed Abbot to avoid withdrawing medically necessary products from the market

Consent decrees – Schering-Plough

- Imposed for alleged failure to carry out cGMPs at certain facilities
- Prohibited manufacturing, packaging and distributing many drugs, except those identified as “medically necessary”
- Required recall of certain products

Consent decrees – Schering-Plough

- Provided for disgorgement of $500 million plus, if product validation was not completed on time, 24.6% of net sales of those products
- Assessed $15,000/day fine for failure to meet timelines for improvement
- Required company to submit written comprehensive cGMP workplan with timetable

Consent decrees – Schering-Plough

Expert Consultant

- Inspects facility and manufacturing processes and controls
- Reviews investigations of out-of-specification test results
- Audits all variances affecting drug safety, identity, strength, quality or purity
- Certifies that all specifications, requirements and workplan comply with cGMPs

Consent decrees – Schering-Plough Validation Studies

- Validation studies required for drug product formulations, dosage forms, strengths, and packaging configurations
- Validation study conduct and results must be certified by expert consultant

Consent decrees – Schering-Plough
Management Controls

- Four qualified people required to monitor and report on employee compliance with cGMP workplans and company SOPs
- Expert consultant must report on adequacy of management controls of manufacturing and laboratory operations and personnel

Consent decrees – Wyeth-Ayerst Labs

- Imposed for alleged failure to carry out cGMPs at certain facilities
- Provided for disgorgement of $30 million and forfeiture of seized articles
- Assessed $15,000/day fine for failure to meet timelines for improvement plus, if actions not completed on time, 18.5% of net sales of certain products

Consent decrees – Wyeth-Ayerst Labs Expert Consultant

- Conducts comprehensive and ongoing facility inspections
- Evaluates company's QA/QC program, production and process controls, records management system, equipment, and validation procedures
- Reports to FDA on company's actions and compliance with timetable
- Certifies that company has satisfactorily completed all actions in the timetable

Consent decrees – Wyeth-Ayerst Labs
Expert Consultant

- Conducts batch record review
- Reports on occurrence, adverse effects, and investigation of deviations from SOPs or atypical environmental conditions
- Reports on management controls
- Assesses company's QA/QC programs

Consent decrees – Wyeth-Ayerst Labs

- Qualified QA/QC employee must monitor and report to company management on employee compliance with cGMP workplans and company SOPs.
- Company must submit validation plan.
- Expert consultant must review and evaluate all validation protocols for validation studies, and certify adequacy of completed studies.

Import Alerts

- Issued by FDA when it believes that products imported from a particular country, manufacturer or shipper show a pattern of violations
- To remove the alert, the company must demonstrate that the problem no longer exists

Preclusion of government contracts

- FDA issues recommendations concerning procurement awards
- Recommendations apply to contracts with government agencies that procure FDA-regulated products
- FDA issues an unacceptable evaluation when cGMP deficiencies are serious enough to support an FDA enforcement action

Criminal investigations for cGMP violations

- Can proceed simultaneously with civil injunction or seizure
- Lets FDA hold individual executives criminally accountable for cGMP violations

Criminal investigations for cGMP violations

- Potential consequences
  - Jail time
  - Restitution to consumers
  - Disgorgement of profits
  - Negative publicity
  - Fine

Criminal investigations for cGMP violations

- Misdemeanor: conviction for a first offense of violating the Federal Food, Drug, and Cosmetic Act, if there was no intent to defraud or mislead
- Felony: commission of a prohibited act after a previous conviction or commission of a prohibited act with intent to defraud or mislead

Criminal investigations
U.S. v. Copanos

- Defendant charged with
  - Misbranding a drug by omitting adequate directions and ingredients from the label of an injectable penicillin product, and
  - Failing to comply with cGMPs.
- Government recommended three years imprisonment and fine of $260,000 for company owner.
- The government argued that for any punishment to be meaningful, it must include a lengthy period of incarceration.

Surviving an FDA inspection

- Preparing for an inspection: have an FDA Inspection SOP in place
- The FDA inspection is limited to facilities where drugs are manufactured or stored, including equipment, finished and unfinished materials, containers and labeling

Surviving an FDA inspection

- FDA may inspect records relating to
  - cGMPs; and
  - Pre-market approval application(s).

Surviving an FDA inspection

- FDA may NOT inspect
  - Financial data;
  - Sales data (other than shipping data);
  - Pricing data;
  - Personnel data (except for qualifications of technical and professional personnel);
  - Research data (other than new drugs);
  - Shipping records;
  - Internal audit reports; and
  - Reports and memos on factory inspections.

Surviving an FDA inspection:
Arrival of the FDA investigator(s)

- The receptionist:
  - Asks the investigators to sit in the lobby
  - Immediately contacts Management
  - If Management is unavailable, asks investigator to either wait or return when these personnel are in the facility
  - Refuses to sign anything, allow inspection of documents, or give out copies of documents

Surviving an FDA inspection:
Receiving the investigators

- The inspection team (escorts)
  - Asks to see the investigator's credentials
  - Asks to see the Form 482
  - Has investigators sign the guest register
  - Tries to determine if any investigator is from FDA's Office of Criminal Investigations

Surviving an FDA inspection

- During the inspection
  - Do not say anything that could be considered as consent for a search
  - Identify a core group of employees to be responsible for the search
  - Segregate privileged files from others

Surviving an FDA inspection:
During the inspection

- Take detailed notes
- Record the purpose of the visit
- Try to learn if the visit is
  - A routine inspection
  - A survey
  - A complaint follow-up
  - A pre-approval inspection
  - In anticipation of any enforcement or regulatory action

Surviving an FDA inspection:
Try to establish ground rules

- The investigator should be escorted at all times
- All requests for documentation, data or product samples, etc, are made through the escort
- Determine a schedule of events or at minimum the areas to be covered and approximate time of day

Surviving an FDA inspection:
Problems and Corrective Actions

- Ask investigators to identify problems noted during the course of inspection so that they may be corrected as soon as possible
- When the investigator notes a problem
  - Immediately inform the appropriate company employees
  - Try to correct before the inspection concludes

Surviving an FDA inspection:
Problems and Corrective Actions

- If the problem is corrected during the inspection
  - Tell the investigators when the corrective action is taken
  - Ask the investigators to either not mention the problem on the Form 483 or to indicate that the problem was corrected during the inspection

Surviving an FDA inspection:
Investigator interaction with employees

- FDA has no authority to compel employees to answer questions posed during an inspection.
- To show cooperation, authorized persons may answer questions that are not inappropriate or leading.
- Escort should tell the investigator that other employees are not authorized to speak for the company.

Surviving an FDA inspection:
Investigator interaction with employees

- Do not joke with the investigator!
- Do not volunteer information
- Do not speculate why the investigator is conducting the inspection
- Always tell the truth!
- Ask for clarification when necessary
- Do not argue or make threatening remarks

Surviving an FDA inspection:
Inspection parameters

- Requests to inspect areas or data beyond the investigator's authority must be made in writing
- Inspections must be at reasonable times, within reasonable limits, in a reasonable manner
- Investigators may not breach sterility or intervene with the production process

Surviving an FDA inspection:
Requests for documents or samples

- Employees should be forbidden to sign or initial any affidavit, receipt for samples or any other document without counsel's approval
- If samples are provided, get a receipt specifying the code, lot number and number of units taken
- Duplicates of all samples taken by the investigator must be taken by the company and identified by lot number, date and correspondence to FDA sample

Surviving an FDA inspection:
After the inspection

- Do not commit to any corrective action unless employees are certain the commitment can be met
- Follow up to assure that required actions are completed expediently
- Prepare responses to any Form 483 observations or other written FDA notices that require written response

Surviving an FDA inspection: The “nonroutine” visit

- If investigator does not have a Form 482 Notice of Inspection, the company’s voluntary consent is required to inspect
- Investigators should remain in the lobby while the inspection team calls the company’s counsel

Surviving an FDA inspection: The “nonroutine” home visit

- Government investigators cannot force employees to consent to interview at home
- Get the name and title of the investigator, and name and location of their FDA office
- Contact company’s legal counsel immediately