

# The Cost of Quality

**USP WCDG & AOAC-SCS  
Regulatory & Compliance Conference  
Irvine, CA  
April 15, 2011**

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# Talking Points

- FDA Roles and Responsibilities
- Globalization of the Pharmaceutical Industry
- Substandard – Definitions and Violations
- Quality Problems Leading to Substandard Products
- Headlines/Fines/Convictions
- Park Doctrine
- Regulatory Outcomes/Business Ramifications
- GMP and Product Quality
- 2010 Top 483 Observations, WL
- Supply Chain and FDA Initiatives
- Summary

# FDA - Roles and Responsibilities

➤ FDA is responsible for:

- Protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation, and by regulating the manufacture, marketing, and distribution of tobacco products.

# FDA - Areas of Coverage

- Food
- Drugs – human and veterinary
- Medical Devices
- Vaccines, Blood, Biologics
- Cosmetics
- Radiation-Emitting Products
- Tobacco Products

# FDA's Reach

- **Are you starting a new business? Do you know if your product is regulated by FDA?**
  - Find answers in the new web resource “FDA Basics for Industry” (<http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm2024416.htm>). This initiative is aimed at improving communication between FDA and industry by making basic information about the regulatory process more accessible to industry in a user-friendly format.
- **How do I know if my product is regulated by FDA?**
  - It depends on what the product is and how it is marketed. For more information, see FDA's general navigation guide for manufacturers of FDA-regulated products and start-ups (<http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm237623.htm>).

# Globalization of the Pharmaceutical Industry

- FDA-regulated products are currently imported from more than 150 countries
  - More than 130,000 importers of record
  - More than 300,000 foreign facilities
- Up to 40% of the drugs Americans take are imported
- Up to 80% of APIs are from foreign sources
- Largest increase in drug manufacturing has been in China and India
- 15 to 20% of all food consumed in the U.S. originates outside US borders
- 70 percent of seafood and about 35 percent of fresh produce consumed in the U.S. come from outside our borders
- Globalization has multiplied the scale of FDA's responsibility; 20M shipments of FDA-regulated products arrived in 2010 at U.S. port of entries

*Margaret Hamburg, speech at Center for Strategic and International Studies, 2/4/10*

# Globalization of the Pharmaceutical Industry

(Cont'd)

- Has led to increased opportunities for:
  - Drug counterfeiting - “Deliberately and fraudulently mislabeling (a drug) with respect to its *identity or source*”
  - Drug diversion
  - Economically motivated adulteration (EMA) - “Fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain”
  - Other intentional acts that can adversely affect quality and safety of pharmaceutical ingredients and drug products

# No Consensus on Terminology for Poor Quality Medicines

- “Counterfeit”
- “Falsified”
- “Substandard”
  - International regulatory agencies cannot agree on the definitions of above-the first step in the collaboration necessary to take action against manufacturers and distributors of poor quality pharmaceutical products

# What is a “Substandard” Medicine?

Proposed revised definition by WHO (10/2010):

- Substandard medicines are pharmaceutical products that **do not meet their quality standards and specifications.**

# Substandard Products in Developed vs. Developing Countries

# In Developed Countries

- National drug regulatory authorities (DRAs) authorize medicines for use based on demonstrated evidence of safety, quality and efficacy.
- Post-approval or authorization, mechanisms are in place to monitor the market to detect and take action on substandard, falsified or unregistered products.

# In Developing Countries

- Effective regulations are not employed due to lack of money, equipment and qualified personnel.
- Some poor countries cannot even maintain a registry of medicines or monitor medicines on the market.
- Per WHO, an estimated 90% of patients buy medicines out-of-pocket (not covered by insurance).
- Patients purchase medicines where they are most affordable, often from unregulated storefront distributors where product is of questionable quality.
- In the absence of government regulation, there is no assurance of product quality or safety even when purchased from a pharmacy.

# U.S. Drug Thefts

- Organized gangs in the U.S. are stealing prescription medicine in increasingly audacious “heists”
  - Lilly’s Enfield, Conn warehouse – subject of largest pharmaceutical theft in history - \$75M worth of cancer, psychiatric and blood-thinning drugs (3/10)
  - GSK Chesterfield, VA - \$6M theft of prescription drugs (8/09)
- 15% of the estimated \$8 - \$12B annual cargo theft in the U.S. are drugs

*Fortune Magazine, April 2011*

# U.S. Drug Thefts (Cont'd)

- Stolen drugs go back in the supply chain; sold to corrupt wholesalers and middlemen and ultimately to pharmacies and on to unwitting consumers
- Drug products can lose potency or degrade under improper storage and inadequate shipping conditions
  - In 2009, ineffective insulin hijacked from a truck was dispensed by pharmacies including Kroger.
    - ✓ Impact: Ohio patient went into convulsions
    - ✓ Impact: Texas patient saw his blood sugar spike

*Fortune Magazine, April 2011*

# Impact of Substandard Medicines

- On Patient: Pose a serious and significant threat to human and public health
- On Regulatory Authorities: Regulatory mechanisms may not be adequate to prevent distribution; in cases where regulatory authority has effective means to stop distribution, drug shortages will occur.

# Drug Shortages

- 77% of the 240 drug shortages reported to FDA in 2010 were sterile injectable products
  - 42% of these were due to product quality issues such as the presence of particulates, microbial contamination, newly identified impurities, and changes in stability.
  - 18% due to product discontinuations
  - 9% were due to issues with raw materials
  - 5% were attributed to manufacturing site shutdown
- Drug shortages cause delay or cancelation of a patient care intervention or medication safety issue/error in patient care
- Shortages resulted in an increase in costs and a market for gray market distributors

*Navigating Drug Shortages in American Healthcare: A Premier Healthcare Alliance Analysis, 3/2011*

# Drug Shortages (Cont'd)

- Legislation proposed by Sen. Amy Klobuchar (D-MN) - **Preserving Access to Life-Saving Medications Act** ([S. 296](#)) (2/2011)
  - The legislation would require drug manufacturers to give early notification to FDA of any incident that would likely result in a drug shortage.
  - The legislation would also direct FDA to establish criteria to identify drugs vulnerable to a shortage and work with manufacturers to establish a continuity of operations plan to address drug shortages.
  - It also requires FDA to perform expedited re-inspections of manufacturers in the case of a drug shortage. If a manufacturer is forced to alter or suspend production due to an FDA-initiated review, the agency must perform a site re-inspection within 90 days once the manufacturer has addressed the underlying situation.

# Substandard Products Violate...

## ➤ FD&C Act

- Prohibited Acts (301)
- Key Adulteration Provisions (501)
- Key Misbranding Provisions(502)
- Key Filing Provision (505)
- Key Import Provisions (801)

# FD&C Act

- Set of laws passed in 1938 giving FDA the authority to oversee the safety of food, drugs and cosmetics.
- Introduction of Act triggered by the sulfanilamide elixir disaster (diethylene glycol used to dissolve sulfanilamide)- resulted in 100 deaths

# Prohibited Acts

- Section 301(a) & (k) of the FD&C Act prohibits:
  - (a) The introduction, or delivery for introduction, into interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded.
  - (k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

# Key Adulteration Provisions (501)

- Definitions of an adulterated drug or device:
  - Contamination – prepared or packed under unsanitary conditions where it may have been contaminated with filth or rendered injurious to health
  - Not meeting official or established specifications
  - Operations do not conform to or are not operated in accordance with GMP; impact on safety, quality, strength, identity of drug
  - Not meeting approved specifications or compendial requirements which impact the strength, identity, purity or quality of drug

# 21CFR Parts 210 and 211

- The failure to comply with any regulation in the manufacture, processing, packing or holding of a drug shall render such drug to be adulterated under Section 501 (a) (2) (B) of the Federal Food, Drug and Cosmetic Act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action *and possible criminal or civil charges (felony and misdemeanor)*.

# Other Key Provisions of the Act

## ➤ Section 502 – Misbranding

- False or misleading label
- Packing and label – inconsistent requirements for designation of drug
- Misleading container

# Other Key Provisions of the Act (Cont'd)

## ➤ Section 505 – New Drugs

- Lacking the required DMF, approved NDA/ANDA/biological or device application
- Not conforming to the conditions of an approved application (CMC, labeling)
- Non-compliance with applicable establishment registration and product listing provisions

## Other Key Provisions of the Act (Cont'd)

- Section 801 – Imports and Exports
  - Imports
    - ✓ Unregistered foreign establishments
    - ✓ Adulteration; misbranding
    - ✓ Refusal of admission

# Use of False Claims Act

- Drug Manufacturers that sell products that do not meet specifications or that fail to report serious adverse events could face False Claims Act allegations and potentially severe penalties in the near future.
- Department of Justice will expand into new enforcement areas. These include:
  - How a drug is manufactured
  - Suppressing safety information
  - Having a particular problem that is an adverse event which is not reported

# Use of False Claims Act (Cont'd)

*“If a drug does not meet specifications and is being sold to a federal government entity, such as Medicare for example, it could be a violation of the Federal Food, Drug & Cosmetic Act and could render the submission of the bill for the drug to be false.”*

Eugene Thirolf  
Office of Consumer Litigation  
Department of Justice  
FDLI Conference, 10/13/09

# Quality Problems Leading to Substandard Medicines

- Poor quality or wrong type or wrong concentration of API
- Poor quality or wrong type or wrong concentration of inactive ingredients
- Poor handling of product during production or distribution
- Failure to sell product prior to expiration date
- Poor stability
- Poor dissolution
- Poor quality packaging/labeling
- Contamination
- Failure to follow GMPs

# Quality Problems Leading to Substandard Medicines (Cont'd)

## ➤ Failure to follow GMPs

- Unintentional due to human error
- Negligence
- Deliberate – cutting corners to save cost

# FDA Regulations

- Food – 21 CFR 110
- Drugs – 21 CFR 210 and 211, 21 CFR Part 11
- Medical Devices – 21 CFR 820
- Vaccines, Blood, Biologics - 21CFR 600; 21CFR 606
- Animals & Veterinary – 21 CFR 500
- Cosmetics - 21CFR 700, 701, 710, 720, 740
- Radiation – Emitting Products - 21 CFR 1000-1050
- Tobacco Products - 27CFR 40

# **Do FDA Regulations Make Pharmaceutical Products Inherently Safer?**

# Do FDA Regulations Make Pharmaceutical Drug Products Safer?

- Pharmaceutical companies regularly fail FDA inspections - increased 483s, WLs
- Companies forced to adhere to manufacturing guidelines or face legal action and the courts
- FDA has levied greater fines on the pharmaceutical firms in recent years for nonconformance to existing guidelines and regulations.

# Fines for Pharmaceutical Manufacturing Violations Make Headlines

- **The FDA fined Schering-Plough Corp. \$500 million** for repeatedly failing plant inspections after the FDA set strict quality control terms on four Schering-Plough facilities. FDA inspectors found "significant violations regulations related to facilities, manufacturing, quality assurance, equipment, laboratories and labeling." According to the Public Citizen's Health Research group, the company shipped out asthma inhalers that contained little or no active ingredient (albuterol) leading to perhaps as many as 17 deaths according to the Public Citizen's Health Research Group. Several massive recalls were the result.
- **Genzyme Corp.**, "Under the consent decree of permanent injunction," agreed to correct manufacturing quality violations at one of its facilities and **will return \$175 million** in "unlawful profits" from the sale of products that were made at the plant. According to the FDA, in addition to failing various QC issues, some products were "contaminated with metal, fiber, rubber and glass particles."
- **Ethex Corp., a KV subsidiary**, pleaded guilty in 2010 to two felony counts stemming from its failure to notify FDA about manufacturing problems involving oversized prescription drug tablets, and agreed to **pay fines and restitution totaling \$25.8 million**.

# Fines for Pharmaceutical Manufacturing Violations Make Headlines (Cont'd)

- **Guidant** reaches agreement with the federal government to plead guilty to medical device reporting violations and **pay a criminal penalty of \$296 million.**
- **Pfizer pays \$2.3 billion** to settle off label promotion
- **GlaxoSmithKline paid \$750 million** in civil and criminal penalties for "knowingly selling contaminated, adulterated and ineffective drugs" produced from its now-closed plant in Puerto Rico. Some of the drugs known to be affected which were produced at this plant were: Paxil, Bactroban, Coreg, Tagamet, and Avandia.

# Enforcement Actions for Pharmaceutical Manufacturing Violations Make Headlines

- *Canadian Drug Maker Apotex Recalls Medications after US Warning, CanWest News Service, 9/18/09*

“Canadian generic drug giant Apotex voluntarily recalled some of its drugs late Thursday following a Health Canada investigation launched last July into the company’s manufacturing processes. The investigation was initiated after U.S. regulators found ‘significant deviations’ from good manufacturing processes during an inspection in Apotex’s Toronto plant.”

- *FDA Seizes Control of 3 J&J Factories, The Daily Targum, March 25, 2011*

“In response to the long list of Johnson & Johnson recalls this past year, which includes Tylenol, the Food and Drug Administration (FDA) took control of three J&J production plants. The FDA took control of the plants through the "consent decree" of McNeil Consumer Healthcare in order to bring the plants up to manufacturing standards.”

# Enforcement Actions for Pharmaceutical Manufacturing Violations Make Headlines (Cont'd)

- *Caraco enters into consent decree with FDA, Reuters, 9/29/09*  
“Caraco Pharmaceutical Laboratories Ltd. said it agreed with US health regulators to resume manufacturing operations at its Detroit facilities only after receiving approval from independent experts and the [FDA]....Production at its Detroit facilities had come to a halt after US authorities in June seized all medicines produced by the generic drugmaker citing repeated violations of manufacturing standards.”
- *Pfizer Sees US Ban on Aurobindo's Facility Hitting Some Suppliers – WSJ, 2/25/11*  
FDA halts import of antibiotic products from Pfizer Supplier Aurobindo for manufacturing problems in Hyderabad, India
- *Dr Reddy's Voluntarily Recalls Some Products from US, New York Times, 9/30/09*  
“India's Dr Reddy's Laboratories Ltd said Wednesday the company is voluntarily recalling four products from the US market as a precaution as some lots contained oversized tablets.”
- *Claris Receives Import Alert Over Contaminants, Pharmalot.com, 11/10/10*  
“Claris Lifesciences, which makes injectables and supplies intravenous bags, was warned by the FDA for a host of significant manufacturing violations at its facilities in which IV bags were contaminated with fungus and bacteria, prompting complaints from customers, including Pfizer.”

# Executive Consequences

## Park Doctrine

- FDA and DOJ are returning to use of the so-called Park Doctrine to prosecute corporate officials whose companies violate the FD&C Act.



# Park Doctrine

- FDA believes the Park Doctrine allows the government to obtain a misdemeanor criminal conviction against a company official for violations of the FFD&C Act **even if**
  - Corporate Official was unaware of the existence of the violation
  - Corporate Official was in a position of authority to prevent or correct the violation AND did not do so
- FDA is training OCI investigators on how to pursue individuals for off-label drug promotion for potential prosecution (*Pink Sheet, April 11, 2011*)

# Signs that Park Doctrine Is Returning

- May 2007 – Purdue Frederick Co. pleaded guilty:
  - Felony charges for misbranding the painkiller OxyContin with intent to defraud or mislead
  - 3 current and former Purdue officials, pleaded guilty to misdemeanor charges as “responsible corporate executives” under Park
  
- They were not charged with having the intent to defraud or mislead.

# Signs that Park Doctrine Is Returning (Cont'd)

- Indictment of former Stryker Biotech President Mark Philip:
  - Specific counts include wire fraud and conspiracy
  - Introducing misbranded or tainted products to the market

# Signs that Park Doctrine Is Returning

(Cont'd)

- KV – Marc Hermelin, the former KV Pharmaceutical Co. chief executive officer banned in 2010 from doing business with the U.S., pleaded guilty in 2011 to violating drug-labeling laws and was sentenced to 30 days in prison. U.S. District Judge E. Richard Webber in St. Louis also ordered Hermelin to pay a \$1 million fine and forfeit \$900,000.

# Regulatory Consequences for Corporations

- Disgorgement of Profits
- Debarment
- Loss of Export License
- Import Alerts – Appearance of Violations
- Exclusion from Medicare and Medicaid
- Senior Corporate Officials appear to be unaware – DOJ, FBI, FDA still holds company responsible
- Withdraw approval of ANDA and other applications

# Potential Business Ramifications

- Loss of consumer confidence in product and brand
- Product recalls
- Supply disruptions and, where disruptions are significant, erosion of market share and capacity to market comprehensive product line
- Impacts on supply agreements
- Risk to pending and approved applications
- Company-to-company litigation
- Consumer litigation
- Spawning of government investigations and legal actions
- Erosion of constructive relationship with FDA and other regulatory agencies
- “Poster Child” impacts

# Potential Business Ramifications (Cont'd)

- Lost or delayed opportunities for growth and profitability due to the misdirection of resources to address the negative consequences from compliance issues stemming from substandard products

# GMP and Product Quality

## ➤ Lessons from the past

- It takes time to understand and apply FDA expectations with respect to cGMP requirements, especially with respect to validation, investigations and documentation

## ➤ Factors influencing sustainable compliance

- Staying current with industry practice and FDA expectations.
- Business demands/competition
- Leadership within the company – vertical and horizontal

# Top 10 FDA 483 Citations in 2010

1. Lack of written procedures describing the roles and responsibilities of the QCU **(211.22d)**
2. Lack of investigations into batches that fail to meet specifications and review of all affected batches **(211.192)**
3. Written production procedures not followed and/or documented at the time of performance **(211.100(b))**
4. Lack of process validation to assure that the drug product has the identity, strength, quality and purity that it is purported to possess (e.g. the production process is not validated for its intended use throughout the life cycle of the product **(211.100(a))**)

# Top 10 FDA 483 Citations in 2010 (Cont'd)

5. Lack of in-process monitoring of critical process parameters (CPPs) that validate the performance of manufacturing processes that cause variability of the in-process materials or drug product **(211.110(a))**
6. Lack of scientifically sound laboratory controls, such as specifications, standards, test methods, sampling plans to assure that components, containers/closures, in-process materials, labeling and drug products conform to standards of identity, purity, quality and strength **(211.160(b))**

# Top 10 FDA 483 Citations in 2010 (Cont'd)

7. Lack of written procedures for cleaning and maintenance equipment used in the manufacturing, process, packaging or holding of a drug product **(211.67(b))**
8. Lack of CGMP training and written procedures **(211.25(a))**
9. Equipment and utensils not cleaned, maintained or sanitized at appropriate intervals to prevent contamination or malfunctions, which would alter the safety, identity, quality, purity and strength of drug product **(211.67(a))**

# Top 10 FDA 483 Citations in 2010 (Cont'd)

10. Lack of testing of drug products to assure products meet final specs and identity /strength of active ingredients prior to release **(211.165(a))**

# Warning Letters

- During the fiscal year 2010 (FY 10, Oct. 2009 until Sept. 2010), 41 Warning Letters were issued, which is 60% more than during FY 09 (only 27 issued Warning Letters).
- The Top 5 deviation ranking shows almost the same results as the years before. Following paragraphs have not been complied with:
  - 211.192 Production record review
  - 211.100 Written procedures; deviations
  - 211.22 Responsibilities of quality control unit
  - 211.160 General requirements (Subpart I - Laboratory Controls)
  - 211.84 Testing and approval or rejection of components, drug product containers, and closures

# International WL

- Laboratory control problems – contributed most of the FDA drug GMP warning letters issued to companies in Asia and Europe in FY 2010.
- Lack of/inadequate SOPs
- Inadequate QA systems
- Deficiencies in records/reports
- Equipment not cleaned/maintained/cleaning validation

# Supply Chain

## ➤ Supplier Management – Critical Issues

- Increasing complexity of supply chain
- Too many suppliers; FDA tracking?
- Questionable suppliers
- Supplier contracts out intermediate synthesis; loss of source traceability
- Inadequate testing – contamination, impurities
- Inconsistent GMPs in all countries; maturation curve
- Language barriers

# How Control of Your Supply Chain Ensures the Quality of Your Pharmaceutical Ingredients<sup>(Cont'd)</sup>

- The manufacturer is ultimately responsible for assuring that processes and systems are in place to ensure control of the quality of purchased materials.
  - Only use trusted suppliers; due diligence
  - Robust supplier qualification program; periodic audits; supply agreements
  - Established presence in foreign country
  - Confirm incoming ingredients
  - Confirm that shipments are not diverted
  - Trust-but verify!

# FDA – Enforcement Strategy

- Key Elements of An Effective Enforcement Strategy
  - The FDA must be:
    - ✓ Vigilant
    - ✓ Strategic
    - ✓ Quick
    - ✓ Visible

*Carmelo Rosa - Acting Branch Chief, Division of Manufacturing & Product Quality, Office of Compliance, CDER - International Compliance Branch– 2009 GPhA/FDA Fall Technical Conference*

# FDA Key Initiatives - GMP

- Set post-inspection deadlines.
- Take responsible steps to speed the Warning Letter process.
- Work more closely with FDA's regulatory partners
- Be prepared to take immediate action in response to public health risks (Risk Control Review).
- Swift, aggressive, and immediate enforcement action; i.e. Prioritize follow-up on Warning Letters and other enforcement actions.
- Develop and implement a formal Warning Letter “close-out” process.

# FDA Initiatives

## Secure Supply Chain Initiative

- FDA's 2-year pilot plan involving 100 applicants (first come-first served), with 5 drugs each. It appears that if applicants can meet certain criteria for these drugs to provide assurance of supply chain integrity, they will have an easier time gaining entry to US ports. - Final FR notice sometime in 2011.
- Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting (PREDICT) - risk-assessment tool to ensure the safety of imported food and drugs. The web-based PREDICT system will rank the risk hazards of food and drugs as they enter the country and allow inspectors to focus on the most likely threats to public health. PREDICT import system is currently used in only 4 districts, but a wider rollout will begin possibly this summer.

*John Verbeten, Import Director, ORA, FDLI Meeting, 4/5-6/11*

# How Do You Stay Current?

- FDA/EMEA Websites
- Trade Associations – PDA, PICS, ISPE, PhRMA, APS
- ICH
- Internet, Blogs, Social Networks
- Press – Pink, Gold, Tan, Silver Sheets, Newspapers
- Personal Contacts – FDA, EMEA, Companies

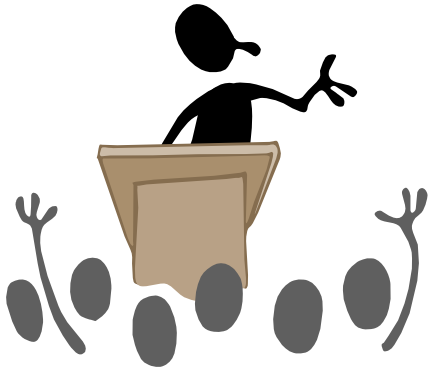
# What Do You Need to Know?

- Regulations and guidances
- How Regulators Enforce the Law
- Compliance from Discovery to Post Marketing Surveillance
- Management Controls – Real Definition
- Crisis Management – Focus on Priorities

# Summary

- The impact of substandard pharmaceutical products is global
- International regulatory agencies need to work together to harmonize international requirements, share information and mitigate risk
- Corporations need to adhere to legal requirements designed to protect product quality and integrity
- Is Quality Worth the Cost? – you be the judge

# Thank You!



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