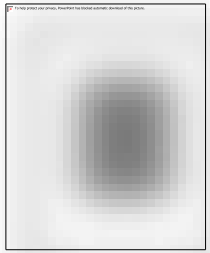
Baker McKenzie.

The Silent Killer: How A Poor Quality System Could Adversely Impact Your Business. An Overview of Hot Issues in Manufacturing and Supply Chain

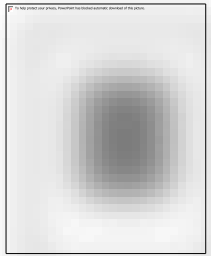
Thursday, September 9, 2021

ACC Association of Corporate Counsel
NATIONAL CAPITAL REGION

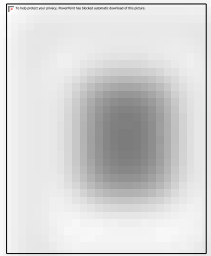
Speakers



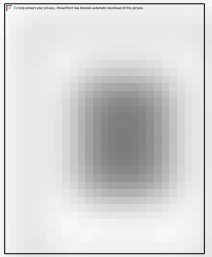
Karen Gally
ACC NCR Committee Co-Chair



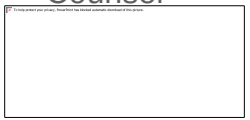
Sabrina Mays-Diagne
Otsuka America Pharmaceutical, Inc.
Associate General Counsel



Veleka Peeples-Dyer
Baker McKenzie
Partner



Samantha Wilson Jones
Spark Therapeutics, Inc.
Associate General Counsel



Agenda

1. WELCOME & INTRODUCTIONS
2. OVERVIEW OF cGMP FOR FDA REGULATED PRODUCTS
3. ENFORCEMENT ACTIVITY
4. PROACTIVE STRATEGIES TO AVOID COMMON PITFALLS

FDA

Mission: responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

Headlines

FDA inspectors find "brown residue" and other violations in plant making Johnson & Johnson vaccine

APRIL 22, 2021 / 6:41 AM / AP

CORPORATE INTEGRITY AGREEMENT
BETWEEN THE
OFFICE OF INSPECTOR GENERAL
OF THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
AND
GLAXOSMITHKLINE LLC

I. PREAMBLE

GlaxoSmithKline LLC (GSK) hereby enters into this Corporate Integrity Agreement (CIA) with the Office of Inspector General (OIG) of the United States Department of Health and Human Services (HHS) to promote compliance with the statutes, regulations, and written directives of Medicare, Medicaid, and all other Federal health care programs (as defined in 42 U.S.C. § 1320a-7b(f)) (Federal health care program requirements) and with the statutes, regulations, and written directives of the Food and Drug Administration (FDA requirements).

Contemporaneously with this CIA, GSK is entering into Settlement Agreements with the United States. GSK will also enter into settlement agreements with various States (State Settlement Agreements) and GSK's agreement to this CIA is a condition precedent to those agreements. Effective October 26, 2010, GSK entered into a Settlement Agreement with the United States to resolve allegations regarding certain drugs manufactured at SB Pharmco's Cidra, Puerto Rico facility.

Whistleblower: FDA downplayed safety issues at Merck vaccine plant

By Brian Buntz | April 2, 2021

A former FDA inspector accused the agency of downplaying safety problems at a Merck plant tapped to manufacture Johnson & Johnson's COVID-19 vaccine.

FDA U.S. FOOD & DRUG ADMINISTRATION

The whistleblower alleged that a 2018 inspection uncovered evidence that employees in the facility in Durham, N.C. engaged in a host of unsanitary practices. A letter to President Biden from the U.S. Office of Special Counsel regarding the Merck plant accuses the company of hiding evidence of employees urinating and defecating in their uniforms rather than taking restroom breaks, which would have required them to leave the manufacturing area and change uniforms.

FDA U.S. FOOD & DRUG ADMINISTRATION

Kansas City District Office
8050 Marshall Drive - Suite 205
Lenexa, Kansas 66214-1524
913-495-5104

February 14, 2017

WARNING LETTER

Ref: CMS Case: 506761
DELIVERY VIA UPS

Mr. Ian C. Reed Chairman and CEO Pfizer Inc.
235 East 42nd St. New York, NY 10017

Dear Mr. Reed:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hospira Inc., a Pfizer Company at 1776 Centennial Drive, McPherson, Kansas, from May 16 to June 8, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Recipient:
Mr. Albert Bourla
Chairman and Chief Executive Officer
Hospira Healthcare India Pvt. Ltd.
235E 42nd St.
New York, NY 10017
United States

Issuing Office:
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Dear Mr. Bourla:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hospira Healthcare India Pvt. Ltd., at Plots B3, B4, B5 (pt); B6 (pt); B11-B18 and B21-B23, SIPCOT Industrial Park, Irungattukottai, Sriperumbudur, Kancheepuram District, Tamil Nadu, India, from March 27 to April 3, 2018.

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1

cGMP for FDA-Regulated Products:

What is it and why does it matter?

Introduction to cGMP for FDA-regulated products

- FDA works to ensure the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations.
- Human and veterinary drug products generally: 21 CFR Parts 210 and 211
    - Manufacturing, processing, packing, or holding drugs (21 CFR 210)
    - Finished pharmaceutical products (21 CFR 211)
- Biologics: Biological products (21 CFR 600)
- Devices: Quality System Regulation (QSR) (21 CFR Part 820)

Management Responsibility

- QS Regulation requires management to establish policies and objectives for ensuring quality (“Management Responsibility” - 21 CFR 820.20)
- Management responsibility requires:
    - Establishing a quality policy, objectives, and procedures
    - Establishing and maintaining “organizational structure”
    - Conducting management reviews

QMS Elements

Enforcement

What could things go wrong?

Headlines

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Hospira Healthcare

- Failure to investigate unexplained discrepancies or batch failure
- Failure to establish valid in-process specifications
- Failure to follow written procedures designed to prevent microbiological contamination of drug products
- Failure to have appropriate laboratory determination of conformance to drug product specifications
- Failure to control reject in-process materials under quarantine
- Lack of complete data in laboratory records

Four Most Common Observations in 2020

*Latest area of focus - data integrity

- Procedures not in writing, fully followed (21 CFR 211.22(d))
- Investigations of discrepancies, failures (21 CFR 211.192)
- Scientifically sound laboratory controls (21 CFR 211.160(b))
- Absence of written procedures (21 CFR 211.100(a))

FDA Inspections in 2021

Document-based inspections leading to GMP violations

01

January 22, 2021

Yuyao YiJia Daily Chemical

Ningbo, China

Not testing materials; inadequate testing of finished products

02

March 10, 2021

Dibar Nutricional S. de R.L. de C.V.

Morelia, Mexico

Inadequate equipment maintenance and testing of components

03

March 10, 2021

Foshan Biours Bioscience

Foshan, Guangdong, China

Inadequate cleaning procedures; not testing finished products

04

April 13, 2021

Proquimes S A Productos Quimicos Especializados S.A.

Cali, Columbia

All drugs placed on an import alert

FDA Enforcement : Inspections

- Inspections generally conducted by FDA investigators who are from one of FDA's field offices
  - May be assisted by other specialists, like laboratory experts or microbiologists
  - Also perform inspections outside the US for products that will be marketed and sold in the US

- Previous inspection history is important, as inspectors will review reports, communications and other information prior to undertaking a new inspection
  - 483s and progress on CAPAs
  - Concerned with any consistent/continuing non-compliance – looks for trends
  - Manuals Used: Investigations Operations Manual (guides the investigators through procedures); and Compliance Program Guidance Manual (inspection procedures for various industries)

Enforcement – Documents provided during FDA Inspection

- ***Notice of Inspection - FDA Form 482***
- ***Observations of Inspection – FDA Form 483***
- ***Receipt of Samples – FDA Form 484***
- ***Affidavit – FDA Form 463***

FDA Enforcement: Inspections

- **Scope of review (21 USC 704(a)(1))**
  including records related to misbranding or adulteration

  exclusions: financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualification of technical and professional personnel performing functions), and research data (other than data relating to new drugs and antibiotic drugs)

- **Drug manufacturing records** (21 USC 374(a)(4)) analyzed for compliance with:

  - **21 USC 351(a)(2)(A)** (to ensure that the drugs are not under insanitary conditions and contaminated or rendered injurious to health);
  - **21 CFR Parts 210** (CGMP in Manufacturing, Processing Packing and Holding of Drugs) and 211(CGMP for Finished Pharmaceuticals);
  - **Draft guidance for compounded drugs**; and
  - **Guidance for active pharmaceutical ingredients**

Enforcement - Potential Consequences

- ***Administrative Detention*: 21 USC 334(g)**
- ***Seizure*: 21 USC 334(a)**
- ***Injunction*: 21 USC 332**
- ***Debarment*: 21 USC 335a**

Enforcement – Additional Ramifications

The Enforcers

FDA

The States

DEPARTMENT OF JUSTICE

FEDERAL TRADE COMMISSION
FOR THE CONSUMER

SECURITIES AND EXCHANGE

Private
Plaintiffs/
Attorneys

Competitors

Proactive Strategies:

Can pitfalls be avoided?

Step #1

Quality Management Systems

A robust Quality Unit supported by Executive Management is the basis for the implementation and continuation of the Quality Management System (QMS).

A Global Quality System is designed to direct and control how quality compliance is implemented and achieved within the organization.

QMS supports business initiatives and objectives in a regulated industry.

QMS Elements

Step #2

Stay Ready!

Routine Audits

- Internal
- CMO / Vendors / Suppliers
- Third Party

Mock Exercises

- Recalls
- Inspections
- Crisis Management

Pre-Inspection Activities

- Inspection Team
- Document Management

Post-inspection Activities

- Response Team
- Document Management
- CAPA Management

Step #3

Be agile!

- Technology
  - Databases (QMAS+, ComplianceWire, etc.)
  - Systems integration (validation requirements)
  - Virtual modeling
- Lessons learned during COVID
  - Virtual inspections are here to stay
  - Supply chain complexity
  - Heightened public awareness

Questions

Select FDA Guidance Documents

- Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers: Guidance for Industry: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-supply-chain-and-drug-and-biological-product-inspections-during-covid-19-public-health
- Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency Guidance for Industry: Guidance for Industry: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid

Guidance for Industry: Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19): https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-temporary-policy-preparation-certain-alcohol-based-hand-sanitizer-products-during

Questions and Answers on Current Good Manufacturing Practices for Drugs: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-current-good-manufacturing-practices-drugs

Notifying CDRH of a Permanent Discontinuance or Interruption in Manufacturing of a Device Under Section 506J of the FD&C Act During the COVID-19 Public Health Emergency (Revised): Guidance for Industry and Food and Drug Administration Staff: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-cdrh-permanent-discontinuance-or-interruption-manufacturing-device-under-section-506j-fdc

Remanufacturing of Medical Devices: Draft Guidance for Industry and Food and Drug Administration Staff: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remanufacturing-medical-devices


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