HOT BUTTON AREAS FOR FDA ENFORCEMENT

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Agenda

- Goals of FDA Enforcement
- Relevant Offices
- Available Enforcement Tools
- Regulatory Priorities and Trends
Goals of FDA Enforcement

- Protect public health by promptly intercepting unsafe or fraudulent products, and preventing additional harm
- Deter others who might violate the law
- Inform the public of potential harms
- Create a level playing field for industry
- Instill public confidence in FDA
Relevant Offices

- **FDA’s Office of Regulatory Affairs (ORA)**
  - Lead office for all agency field activities
  - **Associate Commissioner for Regulatory Affairs (ACRA):** Melinda K. Plaisier
  - Inspects regulated products and manufacturers, conducts sample analyses of regulated products, and reviews imported products offered for entry into the U.S.
  - Located in 5 Regional Offices, 20 District Offices, 13 Laboratories, and more than 150 Resident Posts and Border Stations
Relevant Offices

- FDA’s Office of Criminal Investigations (OCI)
  - **Director:** John Roth (pending confirmation as DHS IG)
  - **Mission:** “[P]rotect[ ] the public health and furthers the FDA mission by investigating suspected criminal violations of the Federal Food, Drug, and Cosmetic Act (FDCA) and other related laws.”
  - Uses traditional law enforcement methods and investigative techniques
    - Obtain and execute arrest and search warrants
    - Carry firearms
    - Gather evidence
Relevant Offices

**CDRH Office of Compliance**

- Reorg in Nov. 2013
  - Director: Steve Silverman
  - Deputy Director for Medical Affairs: Dr. Kimber Richter
  - Deputy Director for Regulatory Affairs: Jan Welch

- Five Divisions:
  - Analysis and Program Operations (DAPO)
    - Review of trends, looking at recall data
  - Bioresarch Monitoring (DBM)
  - International Compliance Operations (DICO)
  - Manufacturing and Quality (DMQ)
    - Focus on quality integration, not just enforcement
  - Premarket Labeling and Compliance (DPLC)
    - Currently 2 people; plans for 20 staff members
Relevant Offices

CDER Office of Compliance

- **Acting Director:** Carol Bennett
- **Offices within the Office of Compliance:**
  - 1. Drug Security, Integrity, and Recalls (ODSIR)
    - Uses risk- and science-based policy development, surveillance, and enforcement to promote the quality, integrity, and security of human drugs for U.S. consumers.
  - 2. Manufacturing and Product Quality (OMPQ)
    - Performs routine inspections and compliance evaluations to ensure compliance with Good Manufacturing Practices (GMPs).
  - 3. Scientific Investigations (OSI)
    - Audits and verifies clinical trial data submitted to FDA supporting approval applications; directs inspections of IRBs for compliance with rules, standards, and regulations related to human subject protection; ensures clinical research organizations, employees, and sponsors comply with good clinical practice and good laboratory practice laws and regulations.
  - 4. Unapproved Drugs and Labeling Compliance (OUDLC)
    - Uses scientific, risk-based strategies, and comprehensive compliance, in an effort effort to eliminate exposure to unapproved or misbranded drugs.
CDER Office of Prescription Drug Promotion (OPDP)

- **Director:** Tom Abrams
- **Mission:** “To protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers.”
On February 3, 2014, Commissioner Hamburg announced a “realignment” project to centralize enforcement at the agency.

- Adding more “specialized” people to the FDA workforce.
  - Affects investigators, compliance officers, import reviewers, laboratory personnel and managers
- ORA will be working with the centers to develop new compliance policies and enforcement strategies
- Management and review levels will be “de-layered” to speed up turnaround time in enforcement actions and decisionmaking
  - Each Center Director will create an action plan by October 1.
AVAILABLE ENFORCEMENT TOOLS
Available Enforcement Tools

- Administrative
  - Civil monetary penalties
  - Clinical Hold
  - Application Integrity Program
  - Debarment
  - Clinical Investigator Disqualification
  - Import detention
  - Untitled and Warning Letters
  - Publicity
  - Recall (“voluntary” and mandatory)
Available Enforcement Tools

- Court-involved
  - Seizure
    - Against the goods themselves
    - Owner must intervene to defend the goods
    - If FDA prevails in court, the goods are usually destroyed
Available Enforcement Tools

- Court-involved (cont.)
  - Injunction
    - Against the company and individuals
    - Intended to compel compliance and prevent future violations
    - Resolved using consent decrees
      - Usually requires significant compliance and monitoring measures (like provisions contained in Corporate Integrity Agreements)
  - Disgorgement and restitution
Evidence-Gathering Techniques

- **Inspections:**
  - Types:
    - Planned pursuant to compliance program
    - Pre-approval inspection
    - “For cause” inspections – follow-up or directed
    - In conjunction with other agencies (state, EPA, other)

  - [Investigations Operations Manual](#)
  - Access to records authorized by statute
  - Interview of witnesses
  - Photographs
Evidence-Gathering Techniques

- **July 2013 Guidance:**
  - Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
  - Explicitly gives investigators the right to take pictures during inspection
  - FDASIA amended statute to add § 501(j) to the Food, Drug, and Cosmetic Act (FDCA) deeming a product adulterated if it was manufactured in any establishment in which the owner delays, denies, or limits an inspection, or refuses to permit entry
Evidence-Gathering Techniques

- OCI has additional powers
  - Trash runs
  - Subpoenas
  - Collaboration with other law enforcement agents
    - Federal Bureau of Investigation
    - Office of Inspector General in the Department of Health & Human Services
REGULATORY PRIORITIES
Advertising and Promotion

- **Drugs (OPDP)**
  - **Number of Warning and Untitled Letters issued in 2013 was slightly less than in 2012**
    - 1 issued as of January 31, 2014
    - 24 issued in 2013
    - 28 issued in 2012
  - **2014 Untitled Letter: Mission Pharmaceuticals**
    - Advertisement failed to mention contraindications for pregnant women, downplayed “Black Box” warning, and made unsubstantiated superiority claims
  - **Notable 2013 Warning Letter: Aegerion Pharmaceuticals**
    - Warning Letter based on statements made by the company’s CEO on MSNBC’s “Fast Money” television show, whose target audience is the investment community
Advertising and Promotion

- **Drugs (cont.)**
  - OPDP has recently focused on claims made in company press releases
    - 10/18/2012 – Burzynski Research Institute – online press release
    - 10/31/2012 – Cornerstone Therapeutics – pitch letter and press release
    - 02/21/2013 – ParaPRO, LLC – video news release
    - 12/16/2013 – Amarin Pharmaceuticals Ireland, LLC – webcast invitation
  - Between 2001 and 2012, OPDP issued only one letter related to news releases
    - 10/08/2009 Warning Letter – King Pharmaceuticals, Inc. – video news release
Advertising and Promotion

- Devices
  - **Focus on company websites advertising products without FDA approval or clearance**
    - Warning Letters issued to manufacturers of Hyperbaric Chambers (Class II device)
      - 9 Warning Letters citing this violation based on website review since 2001
      - 6 of these were issued between June and August 2013
        - 06/25/2013 – Andi International
        - 08/08/2013 – Healing Dives, Inc.
        - 08/08/2013 – Hyperbaric Options
        - 08/08/2013 – The Reynolds Office of Health and Nutrition
        - 08/08/2013 – Pressure Tech Inc.
        - 08/08/2013 – OxyHealth LLC
  - Warning Letters all state that FDA may take enforcement action without notice if not corrected, including injunction and seizure
Advertising and Promotion

- **Devices (cont.)**
  - Joint FDA/FTC Untitled “E-mail”
    - February 2013 letter from FDA/FTC to online distributors of decorative contact lenses
      - FDA considers products adulterated or misbranded if they are unapproved
      - FTC considers sale without a valid prescription as violation of Fairness to Contact Lens Consumer Act, and the Contact Lens Rule – civil monetary penalties
      - Based on OCI and FTC review of companies’ websites
    - Threatens possible criminal action, unlike typical “Untitled Letters”
Advertising and Promotion

- Devices (cont.)
  - Focus on elective cosmetic surgical centers
    - 2011 Warning Letters for LapBand gastric banding system for weight loss
      - Not directed to Allergan – maker of LapBand – but to the surgical centers
      - Alleged to be misbranded because advertisements failed to disclose information describing risks associated with LapBand
    - 2012 Warning Letters for LASIK products
      - As with LapBand products, letters were directed to surgical centers
      - Alleged that advertisements failed to disclose key risk information
Pharmacy Compounding

- April 2013 statement regarding inspection assignments that identified 29 pharmacies as priority inspections
- FDA issued Form FDA-483s to all but one pharmacy
  - Incomplete and/or inadequate drug product batch failure investigations
  - Inappropriate clothing for sterile processing
  - Lack of appropriate air filtration systems
  - Insufficient microbiological testing
- Question of FDA authority to regulate pharmacy compounding; 483s address cGMP violations
Pharmacy Compounding

Compounding Quality Act (enacted November 2013)
- Clarifies FDA’s authority to regulate compounding pharmacies
- FDA’s plans for implementation set forth on [website](#)
- Draws distinction between traditional compounding pharmacies (individual, per patient) and large-scale compounding pharmacies (like NECC) that ship products across state lines (“outsourcing facilities”)
  - “Outsourcing facilities” would be regulated by FDA, but exempt from regulations applicable to traditional pharmaceutical companies

First Warning Letters under Act issued in January 2014
- Based on inspections that occurred before the Act’s enactment
- Violation of FDCA § 503A, compounding drugs without valid prescriptions, in addition to other cGMP violations
Manufacturing Practices

- Inspectors cite inadequacies in procedures more often than product defects/failures and responses thereto

  - Most prevalent in devices:
    - (1) failure to develop corrective and preventive actions (CAPA);
    - (2) failure to establish complaint procedures;
    - (3) failure to craft and utilize adverse event reporting procedures;
    - (4) failure to create procedures for determining whether materials conform to specifications.
Delinquent User Fees

- Failure to self-identify its finished dosage form (FDF) manufacturing facility and pay user fees
  - September 17, 2013 Warning Letter to Germany-based C.P.M. Contract Pharma
  - Penalties include:
    - Identification on publicly available arrears list; FDA will not receive any new applications from person on list
    - FDA will not receive any new generic drug submissions that reference a non-compliant facility
    - All FDF or API manufactured at the facility is deemed misbranded under FDCA § 502(aa)
  - FDA threatens further regulatory action, including seizure, injunction, import alert
Drug Supply Chain (Track & Trace)

Drug Supply Chain Security Act (enacted November 2013)

- Requires electronic, interoperable pedigree system to be in place in 10 years
- Contains licensure requirements for manufacturers, wholesalers, repackagers, and dispensers (e.g., pharmacies), and 3rd Party Logistics providers
- Requires multiple guidance documents, public meetings, and pilot programs from FDA

Some provisions took effect on the date of enactment, but FDA still has not issued regulations.
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