Off-label Promotion: Enforcement Tools and Trends

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Off-Label Enforcement Primer
The Basics

The FDCA prohibits manufacturers from:

- Promoting products before they are cleared for marketing,
- Promoting products off-label, and
- Otherwise promoting products in violation of FDA regulations (e.g., non-truthful, misleading, risk minimizing)

“Promotion” not defined in the regulations
## Major Settlements in Off-Label Investigations

<table>
<thead>
<tr>
<th>Company</th>
<th>Settlement Amount</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech (HGH)</td>
<td>$50 million</td>
<td>1999</td>
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<tr>
<td>TAP (Lupron)</td>
<td>$875 million</td>
<td>2001</td>
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<tr>
<td>Pfizer (Lipitor)</td>
<td>$49 million</td>
<td>2002</td>
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<tr>
<td>AstraZeneca (Zoladex)</td>
<td>$354.7 million</td>
<td>2003</td>
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<tr>
<td>Warner-Lambert (Neurontin)</td>
<td>$430 million</td>
<td>2004</td>
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<tr>
<td>GlaxoSmithKline (Paxil)</td>
<td>$2.5 million</td>
<td>2004</td>
</tr>
<tr>
<td>Eli Lilly (Evista)</td>
<td>$36 million</td>
<td>2005</td>
</tr>
<tr>
<td>Serono (Serostim)</td>
<td>$704 million</td>
<td>2005</td>
</tr>
<tr>
<td>Schering-Plough (Temodar)</td>
<td>$435 million</td>
<td>2006</td>
</tr>
<tr>
<td>Intermune (Actimmune)</td>
<td>$36 million</td>
<td>2006</td>
</tr>
<tr>
<td>Medco (various)</td>
<td>$163 million</td>
<td>2006</td>
</tr>
</tbody>
</table>
**Major Settlements (cont.)**

- Cell Therapeutics (Trisenox): $10.5 million (2007)
- Purdue Pharma (Oxycotin): $654 million (2007)
- Jazz/Orphan (Xyrem): $20 million (2007)
- Cephalon (various): $425 million (2007)
- Pfizer/Pharmacia (Genotropin): $34.7 million (2007)
- Biovail (Cardizem LA): $22.2 million (2008)
◆ Almost $3 billion in the last 3 years alone!!
Who Are The Enforcers?

- Department of Justice/U.S. Attorney’s Offices
- FBI
- FDA-Office of Criminal Investigations
- HHS-OIG
- U.S. Postal Inspectors
- IRS
- SEC
- State Attorneys General
- Congress
- Plaintiffs’ Bar
What’s in the Government’s Enforcement Toolbox?

- Warning letters, injunctions
- Civil action, forfeiture
- Fines, civil penalties, restitution
- CIAs, CCAs, IROs
- Criminal prosecution/incarceration
- Exclusion/debarment
Government Investigative Sources and Techniques

◆ Covert:
  ➢ Informants/cooperating witnesses
  ➢ Consensual monitoring
  ➢ Undercover operations

◆ Overt:
  ➢ Interviews of employees/customers
  ➢ Administrative investigative demands (AIDs) and grand jury subpoenas
  ➢ Whistleblowers
  ➢ Search warrants
Statutes Used to Enforce Off-Label Marketing Prohibition

- The Federal Food, Drug, and Cosmetic Act (FDCA)
- The Federal False Claims Act (FCA)
- The Federal Anti-Kickback Statute
- Securities Laws
- Various State Laws, including State False Claims Acts
The FDCA (21 U.S.C. § 331)

- Prohibits introducing a misbranded drug or device into interstate commerce

- “Misbranding” includes promoting off-label

- “Intent to defraud or mislead” = felony

- Felony and Misdemeanor Criminal Penalties (unusual in federal law)

- *United States v. Park*, 421 U.S. 658 (S. Ct. 1975) – strict liability misdemeanor is permissible in light of the importance of the function of the pharmaceutical manufacturers
False Claims Act
(31 U.S.C. § 3729, et seq.)

◆ Prohibits knowingly presenting (or causing to be presented) to the federal government a false or fraudulent claim for payment
◆ Treble damages + civil monetary penalties
◆ *Qui tam* (or whistleblower) provision
◆ DOJ recovered > $2.2 billion in FY 2006 from health care companies as a result of FCA-related settlements/judgments
Government’s Off-Label Theory of FCA Liability

- Federal health care programs often do not cover drugs for off-label use
- When company promotes drug for off-label use:
  - Causes doctors to prescribe for off-label indications
  - Causes patients to take script to pharmacy
  - Causes pharmacy to submit claim for payment to federal health care program
  - Causes government to pay false claim
- But see *Underwood v. Rhone-Poulenc Pharmaceuticals, Inc.*, 890 So.2d 429 (Fla. 2004) (holding that off label promotion not prohibited by the FDCA and that liability under the Ohio FCA can therefore not be premised on such activity).
Anti-Kickback Statute
(42 U.S.C. § 1320a-7b)

◆ Prohibits offering, paying, soliciting or receiving any remuneration in exchange for referring an individual to another for services or items that may be paid by a federally-funded health care program

◆ Conduct must be “knowing and willful”

◆ OIG “safe harbors”

◆ 5 years in prison + $25,000 fine
SECURITIES LAWS

Section 10(b) of Securities Exchange Act

- Prohibits the use or employ in connection with the purchase or sale of any security
- Any manipulative or deceptive device or contrivance in contravention of SEC rules
SECURITIES LAWS (cont.)

SEC Rule 10(b) – unlawful to:

- Employ any device, scheme or artifice to defraud

- To make any untrue statement of a material fact or to omit a material fact necessary to make the statements not misleading

- To engage in any act, practice, or course of business which operates or would operate as a fraud or deceit upon any person in connection with the purchase of any security.
SECURITIES LAWS (cont.)

♦ Example Cases Involving Off Label Promotion Claims


Some Factors in Enforcement Decision

1. How much money is involved?
2. What percentage of sales is off-label?
3. Did the FDA specifically reject the off-label use being promoted?
4. What did company’s own clinical trials show?
5. Are there adverse health effects from off-label use?
6. Were kickbacks paid?
7. Did promotion include advice on how to obtain reimbursement (codes to use, etc.)?
8. Did company self-report?
Red Flags for Government Investigators

1. Increased rate of off-label prescriptions following event at issue (medical conference, off label detailing, etc.)
2. A small market for approved use relative to a large sales force
3. Absence of clear corporate policies against off-label promotion, compliance training programs, etc.
4. Unrestricted educational grants and funding of unaccredited CME
5. Excessive payments/compensation to CME provider; absence of written agreement
Red Flags for Government Investigators

7. Promotion to medical specialties with no on-label indications for the drug at issue (pretext)

8. Involvement of Sales/Marketing in CME and/or grant decisions; tracking "ROI" for supposedly independent CME programs

9. Speakers Bureaus, Consulting Agreements, Advisory Boards for Marketing
Off-Label Enforcement Update
FY 2007

HHS-OIG: $4.08 billion of expected recoveries
- $1.9 billion in audit receivables
- $2.18 billion in investigative receivables
- 3,308 exclusions
- 262 civil actions
- 447 criminal actions

HHS-OIG Semiannual Report to Congress (period ending 09/30/07)
First Half of FY 2008

HHS-OIG:
- $2.2 billion of expected recoveries
- -$1.1 billion in audit receivables
- -$1.1 billion in investigative receivables
- 1,291 exclusions
- 142 civil actions
- 293 criminal actions

HHS-OIG Semiannual Report to Congress (period ending 03/31/08)
Recent Settlements in Off-Label Investigations

**Biovail Pharmaceuticals, Inc.** (May 2008)

- Subsidiary of Biovail Corp. agreed to plead guilty to conspiracy and kickback charges
- Paying physicians $1000 each to promote or recommend Cardizem LA (heart medication)
- Paid $22.2 million criminal fine
Recent Settlements

**BMS and Otuska Pharmaceuticals** (Sept. 2007 and March 2008)

- BMS and Otuska were co-promote partners for Abilify, an antipsychotic drug approved for bipolar disorder and schizophrenia in adults
- Qui tam actions were filed regarding marketing Abilify off-label for pediatric and geriatric dementia-related psychosis
- BMS was also accused of various other fraudulent drug-pricing allegations relating to some of its other projects
- BMS paid $515 million to resolve all charges
- Otuska paid $4 million to resolve the Abilify allegations
- Both agreed to a CIA
Recent Settlements

**Cephalon Inc.** (November 2007)

- Investigation by US Attorney's Office in Philadelphia and US DOJ
- Alleged off label promotion of Gabitril (epilepsy drug), Provigil (narcolepsy drug), Actiq (cancer pain reliever)
- High sales goals and pushing higher doses
- Pay $425 million to resolve state and federal Medicaid claims
- Plead guilty to one misdemeanor under FDCA
- Enter into CIA
Recent Settlements

**Jazz Pharmaceuticals/Orphan Medical** (July 2007)

- Parallel civil and criminal investigations by US Attorney's Office for Eastern District of NY
- Orphan promoted Xyrem, approved only for narcolepsy, for fatigue, insomnia, weight loss, depression, bipolar disorder and Parkinson's disease.
- Orphan pled to felony misbranding of a pharmaceutical product in violation of FDCA.
- Jazz entered into a non-prosecution agreement, which includes a guarantee of Orphan's $20 million in civil and criminal penalties
- Both Jazz and Orphan also entered into a civil settlement agreement
- Jazz also agreed to a 5 year CIA
Recent Settlements

Medicis Pharmaceutical Corp. (May 2007)
- Civil settlement agreement in FCA case
- Settles charges that Medicis illegally marketed Loprox, approved as a fungicide for people over the age of 10, for diaper dermatitis and other skin disorders in children under 10
- Pay $9.8 million
- 5 year CIA
Recent Settlements

**Purdue Pharma LP** (May 2007)

- Civil and criminal settlement
- Subsidiary pleads guilty to one felony count of misbranding due to off label marketing of Oxycontin by promoting that it was less addictive than other drugs in same class
- Company paid $619.5 million to resolve civil and criminal charges
- Former Chief Scientific Officer, current CEO and GC pled guilty to strict liability misdemeanor and paid an additional $34.5 million in criminal fine
- 5 year CIA
Recent Settlements

**Cell Therapeutics Inc. (April 2007)**

- Settlement of FCA case relating to off label promotion of Trisenox, a drug approved only for refractory or relapsed acute promyelocytic leukemia
- Cell Therapeutics was promoting the drug for other types of leukemia, liver cancer, multiple myeloma and myelodysplastic syndromes
- Allegations regarding kickbacks (*i.e.*, sham consulting agreements and hiring high prescribers to be in the Speakers Bureau).
- Agreed to pay $10.5 million
- Agreed to negotiate a CIA
Recent Settlements

**Pfizer Pharmaceuticals** (April 2007)

- Subsidiary Pharmacia entered into deferred prosecution agreement (DPA) with Govt
- Genotropin approved for treatment of children with hormone-related growth failure
- Pharmacia marketed it to adults for anti-aging and lifestyle enhancement purposes
- Charged with introducing misbranded drug in violation of FDCA
- Paid $15 million criminal fine
Recent Settlements

**Pfizer** (cont’d)

- Flew hundreds of doctors to endocrinology conference in Puerto Rico where new research presented supporting off-label use
- No adverse health effects from off-label use and only 10-15% of revenues from off-label
- Pfizer self-reported to Federal authorities within a month after acquiring Pharmacia
- Pfizer also immediately implemented specific training mechanisms
Recent Settlements

**Intermune** (October 2006)

- Entered DPA and paid $36 million to resolve criminal charges and FCA lawsuit
- Charged with introducing misbranded drug
- Majority of sales due to scripts for off-label use
- Company’s own clinical trials failed to establish statistically any benefit from off-label use
- Under CIA, all speaker programs and funding of or participation in CME activity must comply with FDA requirements (and IRO to audit)
Recent Settlements

**Warner-Lambert** (May 2004)

- Pled guilty to introducing misbranded drug
- Settled FCA lawsuit
- Paid $430 million ($240 million criminal fine + $190 million civil settlement)
- Involved anti-epilepsy drug Neurontin
- Clinical studies showed drug not effective for many of the off-label uses promoted
Recent Settlements

**Warner-Lambert** (cont’d)

- Evidence of coordinated national effort to implement off-label strategic marketing plan:
  - Organized “consultants meetings”
  - Hired “medical liaisons”
  - Sponsored/funded CME events on off-label use
  - Paid some doctors up to $250,000 for favorable messages regarding off-label uses
FDA Activity

◆ **Draft Guidance** — “Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices” (2/2008)

– Response to sunsetting of §401 of FDAMA
Congressional Activity

◆ Response to *FDA Draft Guidance on Good Reprint Practices*

– Rep. Waxman (D-CA) criticized FDA for allowing manufacturers to “short-circuit FDA review and approval” and “put the public at risk for ineffective and dangerous uses of drugs.”

– Rep. Waxman requested documents relating to this guidance from FDA
Congressional Activity

◆ Senate Finance Committee Report: “Use of Educational Grants by Pharmaceutical Manufacturers” (April 25, 2007)

• Result of 2 year inquiry

• Prompted by belief that drug makers using CME to deliver promotional messages (including off-label use) not allowed to do on their own

• Contacted 23 largest drug companies

• Sent questionnaire to ACCME
Congressional Activity

◆ Senate Finance Committee Report (cont’d)

• Critical of corporate policies which allow industry to “walk a fine line”

• Critical of ACCME

  ■ Found that during 2005-2006, nearly 25% of CME providers violated at least one standard

  ■ No real time oversight of programs

• No specific recommendations

• Report expected to further fuel government crackdown on off-label promotion via CME
Congressional Activity

FDA Amendments Act of 2007

- Expands clinical trial registry requirements
  - More information must be submitted
  - Now extends to device companies

- Requires submission of clinical trial results written in “non-technical, understandable language for patients”
Congressional Activity

Physician Payments Sunshine Act of 2007—Senate Bill 2029

- Seeks to amend the Social Security Act to require quarterly transparency reports to the Secretary of HHS of payments to physicians or their employers by manufacturers of covered drugs, devices, or medical supplies under covered Medicare, Medicaid, or State Children's Health Insurance Program (SCHIP).
Physician Payments Sunshine Act of 2008—House Resolution 5605

- Seeks to require quarterly transparency reports to HHS of payments to physicians or their employers, or to a covered organization in which a physician has a significant professional membership interest, by manufacturers of covered drugs, devices, or medical supplies.

- Seeks to amend the Internal Revenue Code to prohibit tax deductions for the advertising, promotion, or marketing by manufacturers of drugs, devices, and medical supplies on whom a penalty is imposed for failing to meet the requirements of this Act.
Tools to Reduce Risks

- OIG Compliance Program Guidance for Pharmaceutical Manufacturers
- FDA Guidance on Industry Support of Scientific and Educational Activities
- PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results
- PhRMA Code on Interactions with Health Care Professionals
- AdvaMed Code of Ethics for Interactions with Health Care Providers
- ACCME Guidelines
- United States Sentencing Guidelines
- McNulty Memorandum – DOJ Principles of Prosecution for Corporations