Prosecutorial Perspective on Off-Label Promotion

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The views expressed are the author's, they are not official policy of the Department of Justice.

Functions of Independent Continuing Medical Education

- Achieve the best possible quality of patient care
- Well-informed medical community
- Provide objective, accurate, complete and appropriate information
- Assure independent medical judgments
- Support medical research and education

Concerns

- Patient safety
- Effective treatment
- Availability and cost of treatment

Legal Framework

- Drug approval: FDCA
- Drug marketing: FDCA, FDAMA and First Amendment
- Anti-Fraud and abuse protections

Food, Drug and Cosmetics Act

- Manufacturer of "new drugs" must demonstrate to FDA that they are safe and effective for each intended use. 21 U.S.C. 331(d)
- 21 U.S.C.331(a) Prohibits distribution of misbranded drug, including where label includes information about unapproved uses

Labeling

- Reviewed by FDA
- Specifies risks and benefits
- Gives indications and claims of benefits
- Pre-clinical and clinical trial results
- Drug must be safe and effective for all proposed claims. 21 CFR 201.100(d)

Promotion

- Claims in promotional “labeling” or advertising must be consistent with approved labeling. 21 CFR 202.1(e)(4)
- False or misleading representations with respect to another drug renders label “misbranded” 21 CFR 201.6

FDAMA

- Narrow safe harbor for manufacturers who clear with FDA in advance the dissemination of journal articles and reference texts under clearly defined conditions
- Evidence disseminated outside safe harbor may be prosecuted and information disseminated may be evidence of manufacturer's actual intended uses for the drug undisclosed to FDA and unapproved by FDA

Balancing Factors: Regulation v. First Amendment

- What the manufacturer may lawfully claim that a drug does, and what a physician may prescribe a drug for, do not match
- First Amendment does not require dismissal of off-label marketing indictment
  - United States v. Caputo, et al, 288 F. Supp. 2d 912 (N.D. Ill. October 21, 2003 (Indictment for marketing of medical device allegedly modified from original FDA-Approved medical device sterilizer allowed to stand)

Balancing (cont.)

- There is a substantial government interest in subjecting even truthful off-label uses to the FDA evaluation process under 21 C.F.R. 801.4.
  - Illinois ex rel Madigan v. Telemarketing Associates, Inc., 538 U.S. 600, 123 S.Ct. 1829 (May 5, 2003)(false and misleading representations to deceive donors can state fraud claim)

FDCA Remedies

- Administrative seizure of drugs. 21 USC 334(a)
- Injunctions against unlawful promotional activities. 21 USC 332(a)
- Production Step-downs
- Criminal Penalties for off-label marketing. 21 USC 333(a)

Justice Department Tools

- Civil False Claims Act, 31 U.S.C. 3729 et seq.
- AntiFraud Injunction, 18 U.S.C. 1345
- AntiKickback Act, 42 U.S.C. 1320a-7b(b)
- Interplay with other substantive statutes:
  - Medicaid Reimbursement statute
  - Prescription Drug Marketing Act
  - Food Drug & Cosmetics Act reporting provisions

Standards

- FDCA: Knowing conduct (felony); Strict Liability (misdemeanor) 21 U.S.C. 333
- Anti-Kickback Act: Intentional conduct
- False Claims Act:
  - Wilful conduct
  - Reckless disregard for truth or falsity
  - Deliberate indifference to truth or falsity
- AntiFraud Injunction: Court Imposes Equity
  - Probable cause to believe fraud occurred
  - Hearsay Evidence; Ex parte applications to court

Anti-Kickback Act: One Purpose Test

- "If the payment was made with multiple purposes, if only one of those purposes was to induce referrals, the payments constitute illegal remuneration." United States v. Greber, 760 F.2d 68 , 71 (3d Cir.), cert. Denied, 474 U.S. 988 (1985)
- Safe Harbor is not a guarantee

False Claims for Off-Label Medicaid Reimbursement

- Medicaid reimbursement available only for "covered outpatient drugs." 42 U.S.C. 1395b(i)(10)
- Covered Outpatient drugs exclude those "used for a medical indication which is not a medically accepted indication." 1396r-8(k)(6) A medically accepted indication includes FDCA approved use or use included in specified drug compendia. 1396r-8(g)(1)(B)(i)

False Claims for Medicaid Reimbursement (Cont.)

- Prescription for off-label use of drug not included in identified compendia is not Medicaid reimbursable.
  - U.S. ex rel. Franklin v. Parke-Davis, 147 F. Supp. 2d 30, 44 (D. Mass. 2001)(Mfrs false statements to doctors caused ineligible off-label prescriptions to be submitted for payment by Medicaid)
  - U.S. ex rel. Drescher v. Highmark, (E.D.Pa.,Feb. 19, 2004)(FCA claims sustained on "caused to be submitted" theory, where primary payer returned claims to provider unpaid, and provider then submitted to Medicare.

Parke Davis Prosecution

- US v. Parke-Davis (Warner-Lambert)(D. Mass. 2004)
  - Guilty plea to Misbranding the drug Neurontin, 21 USC 331(a), 352
  - $430 Million Criminal Fine, damages to Medicaid, and consumer protection remediation in 50 states
  - Corporate Integrity Agreement

Neurontin

- Approved 1993 for epilepsy as supplemental anti-seizure drug
- Marketed to treat: Depression, bipolar disorder, pain, Lou Gehrig's Disease, ADD, migraines, drug and alcohol withdrawal seizures, restless leg syndrome
- Promoted Neurontin even where scientific studies showed it was not effective
  - Monotherapy for epilepsy, specifically rejected by FDA,
  - Bipolar study showed placebo worked as well or better than Neurontin

Neurontin Marketing

- Organized, deliberate, misleading actions to avoid restrictions on marketing unapproved new drugs
- Sales reps gave sales pitches to doctors using false and misleading information about off label uses
- Medical Liaisons, falsely identified as scientific experts, promoted off label uses
- Paid doctors to attend lavish “consultant meetings” about off label uses
- Paid doctors for sales rep to accompany doctor in patient visits

Genentech Prosecution

U.S. v. Genentech, Inc. (N.D.Ca. 1999). Guilty plea to Introduction of Misbranded Drug in Interstate Commerce. 21 U.S.C. 331(a), 352.

Fine $30 million

Restitution to Medicaid and CHAMPUS $20 million

USA v. Genentech, Inc.

Protropin approved and labeled "only for long-term treatment of children who have growth failure from lack of adequate endogenous growth hormone secretion."

Genentech promoted for short stature for which drug not approved under Section 355.

Genentech introduced Protropin into interstate commerce intending it to be used for medical conditions for which it had not been approved and not been shown to be safe and effective.

In so doing, Genentech acted with intent to defraud and mislead FDA.

Off-label Marketing is Actionable under FCA

U.S. ex rel. Franklin v. Parke-Davis, (D. Mass., August 22, 2003)(Saris, J.)

- Falsehoods to physicians about neurontin's safety or efficacy to induce prescription for uses ineligible for Medicaid reimbursement are probative of false claims. Truthful off-label marketing (ineligible for federal safe harbors) accompanied by financial incentives like kickbacks would also suffice as evidence of false claims.
- Where states do not reimburse for off-label prescriptions, a reimbursement request for an off-label, non-compendium prescription constitutes a false claim.

Evidence

Reports of off-label prescriptions before and after physician conferences hosted by mfr

Small market for approved use/Large sales force

Sampling targeted at physicians whose specialty does not include approved use

Financial incentives for off-label use, only

Failure to identify company funding for research, articles, presentations

Promotional claims without scientific basis, untruthful, or unbalanced

Health consequences from off-label use

First Amendment Issues

- Washington Legal Foundation v. Friedman, 13 F.Supp. 2d 51 (D.D.C. 1998)
- Washington Legal Foundation v. Henney, 36 F.Supp. 2d 16, 18-19 (D.D.C 1999)
- Washington Legal Foundation v. Henney, 202 F.3d 331, 335 (D.C. Cir. 2000)
- Illinois ex rel Madigan v. Telemarketing Associates, Inc., 538 U.S. 600, 123 S.Ct. 1829 (2003)