Compliance In Off-Label Promotion: Can Industry Compliance Satisfy the Prosecutorial Perspective?

Margaret L.Hutchinson
Assistant U.S. Attorney
Eastern District of Pennsylvania

T. Reed Stephens
Partner
Sonnenschein, Nath & Rosenthal
Washington, D.C.

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Objectives

- Explore the prosecutorial perspective of Off-Label Promotion practices – is everything suspect?
- Contrast industry and prosecutorial views of specific Off-Label Compliance Issues
- Provide background on the statutory and regulatory framework

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

Prosecutorial Concerns: Labeling Standards

- 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)

Prosecutorial Concerns: Off-Label 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

Compliance Response:

- False or misleading representations with respect to the drug may be examples of misbranding, but it matters who makes the representations
- Manufacturer compliance standards count: manufacturers are not *per se* liable for misstatements by truly independent third party CME providers

Compliance Response: Independent Continuing Medical Education Addressing Off-Label Use Can Be Positive

- Achieve the best possible quality of patient care
- Well-informed medical community
- Provide objective, accurate, complete and appropriate information, and

Positive Aspects of CME – even in the Off-Label Context

- Assure independent medical judgments
- Support medical research and education

Prosecutorial Concerns About Off-Label Use

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

Prosecutorial Concerns: 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)

Prosecutorial Concerns:

- 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.

Prosecutorial Concerns: the Neurontin Scenario

- 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
  - What was the conduct?

The Neurontin Conduct

- 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

The Court's "bright line" Test

Franklin, (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.

Prosecutorial Concerns: Genentech

- 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 in a Global Civil Settlement

Prosecutorial Concerns

- 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.

Prosecutors and Compliance Experts Agree On These Red Flags

- Reports of off-label prescriptions before and after physician conferences hosted by mfr
- Small market for approved use/Disproportionately Large sales force
- Sampling targeted at physicians whose specialty does not include approved use
- Financial incentives for off-label use, only

More Red Flags

- Failure to identify company funding for research, articles, presentations
- Promotional claims without scientific basis, untruthful, or unbalanced
- Health consequences from off-label use

Compliance Response:

- But, if the manufacturer is not disseminating or orchestrating the dissemination of Off-Label information by third parties, how should the government react?
- The promotion, prescription of, and patient's use of drugs for Off-Label uses is, in fact, legal under numerous circumstances
- Medicaid programs do reimburse for Off-Label prescription usage.

Prosecutorial Concerns: Balancing Factors: Regulation v. First Amendment

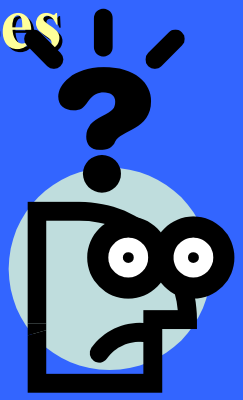
- What the manufacturer may lawfully claim that a drug does, and what a physician may prescribe a drug for, do not match
- First Amendment does not require dismissal of off-label marketing indictment
  - United States v. Caputo, et al, 288 F. Supp. 2d 912 (N.D. Ill. October 21, 2003 (Indictment for marketing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

Prosecutorial Concerns: Balancing, Cont'd

- 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)

Compliance Response:

- The First Amendment does apply, but from a compliance perspective, it provides no immunity from investigation or prosecution. The First Amendment is, therefore, a kind of cold comfort from a compliance point of view.
- The hodge-podge of inconsistent regulatory and judicial statements about Off-Label uses does not represent a regulatory consensus.



Statutory Appendix

- 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)

Statutory Appendix

- 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

Statutory Appendix

- FDCA: Knowing conduct (felony); Strict Liability (misdemeanor) 21 U.S.C. 333
- Anti-Kickback Act: Intentional conduct
- False Claims Act:
  - Willful 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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