Off-Label Use of Prescription Drugs

Legislative & Regulatory Update

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Off-Label Use & Promotion – Basics

- FDA regulates the manufacture, labeling & marketing of Rx drugs
  - Drug manufacturers must obtain FDA approval before they can market their product
  - Drug manufacturer must demonstrate safety & effectiveness of drug for one or more particular uses
  - These approved uses become the **labeled** uses for that drug
  - **Off-label** use occurs when drug is dispensed for a use other than that for which it was approved
- Drug manufacturers are not allowed by FFDCA & FDA **to promote** off-label uses for their products
  - Not allowed to advertise off-label uses
  - Not allowed to induce physicians to prescribe off-label uses
- FDA does not regulate practice of medicine
  - Physicians can prescribe any approved drug for any purpose

How Common is Off-Label Use?

- Off-label prescribing pervasive in oncology
  - 60% of oncologists surveyed reported that they frequently prescribe medications off-label
  - More than half of all cancer patients are treated with drug used off-label
  - Approximately 95% of all oncology drugs are used off-label
- Why so common? Many valuable uses for approved drugs are discovered **post-FDA approval**
  - FDA approval of supplemental NDA takes 2+ years on avg
  - By the time sNDA is approved two-thirds of medical journal articles regarding that use have been published
  - New uses recognized in U.S. Pharmacopoeia on avg 2.5 years before FDA approval

Manufacturer Safe Harbors

- FDA provides certain exceptions & safe harbors for manufacturers
  - **Scientific exchange:** Subject to certain limitations, manufacturers may provide scientific information about new drugs or new uses of approved drugs
  - **Unsolicited requests:** Manufacturers may provide responsive, non-promotional, balanced scientific information in response to an **unsolicited** request
  - **Support for Continuing Medical Education (CME):** Subject to certain limitations, manufacturers may provide support for CME & other scientific & educational activities
  - **Medical journal articles & reference texts:** Under certain circumstances, manufacturers may provide certain types of medical journal articles & medical reference texts

Recent Changes to FDA Policy on Medical Journal Articles (Reprints)

- February 2009 – FDA publishes Good Reprint Practices Guidance
  - Allows drug companies to distribute **unsolicited** reprints that support a particular off-label use of a drug or device
  - Reprints cannot be marked, highlighted, summarized, or characterized by the manufacturer in any way
  - Materials must be accompanied by drug's approved label & distributed separately from information that is promotional in nature
  - Must prominently disclose any author known to the company as having a financial interest in the product or company or who is receiving compensation, along with affiliation of the author and nature & amount of any such financial interest or compensation
- Focus is on greater transparency

Off-label Use & Medicare

- With Medicare & other federal health programs, issue is not whether a physician can administer a drug for such use, but **whether that use may be properly reimbursed**
- November 2008 — CMS issues rule on off-label coverage of cancer drugs under Medicare Part B
  - Prior to Jan 1, 2009, off-label use covered if drug is FDA-approved and use is supported by one or more commonly referenced pharmaceutical compendia (i.e., reference guides used by health care professionals)
  - New rules significantly increased number of reference guides and compendia that could be referenced
- Medicare Part D — more restrictive; only cover off-label use supported in 3 specific compendia

Off-Label Promotion as a Criminal Violation

- Prosecutors have used several legal theories
- Federal Food, Drug & Cosmetic Act (FFDCA)
  - off-label promotion causes drug to become an unapproved "new drug" for that particular use
  - off-label promotion "misbrands" a product. Drug misbranded if does not contain "adequate directions for use" & drug's approved label cannot contain such directions w/respect to any off label use
- Medicare & Medicaid
  - **False Claims Act** – off-label promotion resulting in reimbursement under Medicare & Medicaid constitutes a scheme to obtain money from the government by false or fraudulent pretenses
  - **Federal anti-kickback law** – efforts to promote off-label purchases through gifts, payments, grants, etc. to physicians given in exchange for writing new prescriptions

Sharp Increase in Prosecution for Off-Label Promotion

- DOJ working on more than 200 investigations involving up to 500 drug products for alleged off-label violations
- Fines & settlements at an all-time high for off-label violations -- in past 10 years, feds have collected $12 billion+ in fines prosecuting health care fraud
- Many include *qui tam* (whistleblower) cases involving 3x damages
- Some of the more notable settlements
  - *Eli Lilly* (E.D. Pa. Jan. 2009) — $1.4B for Zyprexa
  - *Cephalon* (E.D. Pa. Sept. 2008) — $425M for Actiq, Gabitril, Provigil
  - *Bristol-Myers Squibb* (D. Mass. Sept. 2007) — $515M for Abilify, Serzone(civil only)
  - *Purdue Frederick Co., Inc.* (W.D. Va. May 2007) — $635M for OxyContin
  - *Pharmacia* (D. Mass. April 2007) — $34.7M for Genotropin
  - *InterMune* (N.D. Cal. Oct. 2006) — $37M for Actimmune
  - *Schering Sales Corporation* (D. Mass. August 2006) — $435M for
  - Temodar, Intron A
  - *Serono* (D. Mass. Oct. 2005) — $704M for Serostim
  - *Warner Lambert* (D. Del. May 2004) — $430M for Neurontin

Recent Changes in Law

- Fraud Enforcement & Recovery Act of 2009
- Signed into law by President Obama on May 20, 2009
- Makes sweeping changes to the False Claims Act
  - Overturns SCOTUS decision in *Alison Engine*, 128 S.Ct 2123 (2008), which held that defendant had to **intend** that his/her false statement or off-label promotion would result in the government paying a false claim. Under new law, liability attaches if the defendant **uses** a false statement to get a false claim paid or approved
  - Includes a "relation back" clause that allows government to take their original complaint, add new claims, but still use the relator's **original filing date** for purposes of the statute of limitations – eliminating an important pharma defense in *qui tam* cases
  - Expands definition of “whistleblower” to include any employee, contractor or agent – effectively overruling a number of cases where certain employees of fiscal intermediaries (e.g., auditors, investigators) were not allowed to seek relief
- Changes likely to increase number of fed investigations & prosecutions alleging off-label promotion

Legislative Activity

- Combating health care fraud & abuse top priority for Congressional Dems & Obama Administration
  - Health care reform legislation — President proposes $500 billion reduction in Medicare spending by reducing "waste, fraud and abuse"
  - June 2009 — President claims potential savings of $300 billion (over 5 years) by eliminating Medicare waste, fraud & abuse
  - September 2009 — President increased potential savings to $500 billion (over 5 years)
  - No details provided on how President expects to achieve these savings
  - Pharmaceutical spending will likely remain key target for additional savings, regardless of $80B PhRMA/Baucus agreement on health reform
- Legislation introduced in 111th Congress addresses other Rx drug marketing practices
  - Physician Sunshine Payment Act (S. 301) — seeks greater transparency in the relationships between physicians & pharmaceutical & device manufacturers
  - Sunshine Act language included in health care reform bill passed by House Energy & Commerce Committee (H.R. 3200) & currently being considered by Senate Finance Committee (America's Healthy Future Act)

Legislative Outlook

- Congress will continue to scrutinize Rx drug industry & practices
- Action on off-label issues in near future unlikely, however, given Congress' focus on health care reform
- Should health care reform pass, focus will be on reducing spending under Medicare, Medicaid & SCHIP
- Rx drug spending will likely remain key target for additional savings, regardless of $80B PhRMA/Baucus agreement
- Follow-on Biologics (FOBs)
  - included in both House & Senate health reform bills
  - higher cost & unique safety concerns associated w/biologics will likely increase congressional scrutiny of off-label use laws & regulations for these products
- Other practices on Congress' radar:
  - Increased use by drug manufacturers of Medical Science Liasions (MSLs) to avoid off-label promotion restrictions
  - Drug manufacturers hiring researchers to "ghostwrite" medical journal articles