



# HORIZONS

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## Specific Focus of Investigations; Specific Lessons from Remedies

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## Specific Focus

- Call lists
- Pediatric
- Oncology
- Geriatric
- Medical and Scientific Liaisons
- Financial Support of CME



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## Lilly

- Press reports (New York Times) said Eli Lilly prepared to settle civil and criminal investigations into marketing of Zyprexa, an antipsychotic drug
- Indicated for severe bipolar disorder and schizophrenia
- Allegation that Lilly encouraged doctors to prescribe for patients with age-related dementia and mild bipolar disorder with prior diagnosis of depression
- Article said Lilly considering \$1 billion fine
- Okay to call on primary care doctors?

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## BMS

- Abilify, atypical antipsychotic, indicated for adult schizophrenia and bipolar disorder
- Allegation: promoted for children and adolescents, or for geriatric patients suffering from dementia-related psychosis
- BMS called on child psychiatrists and other pediatric specialists
- BMS created sales team for nursing homes, where dementia-related psychosis was prevalent
- BMS paid \$515 to settle these and other allegations

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## Corporate Integrity Agreements

- Why do they matter?
- Compliance programs
  - Compliance Officer does not report to CFO or Chief Counsel
  - Anonymous hotline
  - Code of Conduct
  - Training
- IROs
  - Policies and Procedures
  - Verbatims

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## Corporate Integrity Agreements (cont.)

- Ride alongs
- Monitoring
- Verbatims
- Review of all promotional and marketing material, sometimes by outside counsel

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## Other preapproval hotspots

- Read draft guidances
  - 1994 DDMAC on preapproval promotion
  - 2004 “Help-seeking” and disease awareness draft guidance
- Regulation (21 CFR Section 312.7(a) prohibits representing investigational drug as safe and effective, or otherwise promoting the drug
- Medical and Scientific Liaisons
- Support for CME



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## Regulatory Trends and Developments Affecting the Off-Label Promotion of Medical Products

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## Definition of “Off-Label” Use and Promotion

- Uses for a medical product that have not been approved by the FDA are considered “off-label” uses.
- “Off-Label” refers to the requirement for medical product makers to submit product labeling that describes the intended uses of the product to the FDA during the FDA review process. If a use was not included in the submitted and subsequently approved labeling, such use is termed “off-label.”
- Manufacturers are prohibited from advertising, or inducing others to use, medical products for off-label purposes. Such promotion by the manufacturer renders the product misbranded or adulterated.
- Health care practitioners are permitted to make and promote off-label uses of medical products as part of the practice of medicine.

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## Penalties for Off-Label Promotion

- Penalties for manufacturers that promote off-label uses may include:
  - Criminal fines;
  - Civil damages;
  - Exclusion from federal programs; and
  - Disgorgement of profits.
- Other related offenses may result from promoting off-label uses:
  - Some off-label promotions can trigger False Claims Act liability, be considered kickbacks to physicians, or constitute fraud.

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## Impact of Off-Label Considerations on Regulatory Affairs

- Need for accurate and inclusive “intended uses” in FDA submissions.
- Need for careful review of product labels and labeling in FDA submissions.
- Need to review advertising on an ongoing basis for consistency with approved intended uses.
- Need to consider evolving uses when considering enhancements and changes to approved products.
- Need to provide guidance to sales and marketing functions to recognize and avoid off-label promotion.

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## Off-Label Promotion in Health Care Fraud and Abuse Enforcement Activity

- Enforcement activity has increased dramatically in recent years, with focus on:
  - Off-label promotion
  - Kickbacks/remuneration for referrals or business
  - Pricing/price reporting theories
  - Quality/safety as a fraud and abuse issue
- Activities that constitute violations may be subtle, and not fit the typical profile of criminal behavior or abusive practices:
  - Discount pricing practices
  - Payments to consultants – even at fair market value
  - Sales and marketing activities that are common and legal in other industries (e.g., business entertainment)
  - Continuing Medical Education Funding
  - Research funding

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## Fraud and Abuse Laws and Standards

- There are a number of laws relating to fraud and abuse relevant to manufacturers and suppliers:
  - Federal Food, Drug and Cosmetic Act and FDA regulations concerning labeling, promotion and advertising
  - False Claims Act
  - Anti-Kickback Law
  - State law versions of the false claims, anti-kickback and self-referral law
  - State laws regulating marketing of health care products (California Prescription Drug Marketing Act)
  - Stark Law (not directly relevant to manufacturers, but important to know)

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## Enforcement Activity

- Recent Enforcement Actions for Off-Label Promotions:
  - Bristol-Meyers Squibb (Sept 2007: \$515 million dollar fine) Charges included knowingly promoting off-label use of Abilify. \$25 million dollars of the fine represented disgorgement of profits under the Food, Drug and Cosmetic Act.
  - InterMune (October 2006: \$36 million dollar fine) Charges included off-label promotion of Actimmune.
  - Serono (October 2005: \$704 million dollar fine and exclusion from federal health care programs for 5 years) Charges included the off-label promotion of Serostim.
  - Warner-Lambert (May 2004: \$430 million dollar fine) Charges included off-label promotion of Neurontin.
- In each action, other related charges were also brought.

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## Off-Label Promotion

- Despite the penalties, companies may be tempted to promote products for off-label uses:
  - Significant revenue is derived from sales for off-label use.
- Off-label use does not require the manufacturer to conduct expensive, lengthy clinical tests or submit a regulatory application.
- Some off-label uses are valid, and represent the standard of care for certain conditions.

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## FDA Regulation of the Medical Marketplace

- FDA regulates as a “gatekeeper” to the US medical marketplace:
  - Marketing and promotion of a medical product is prohibited until FDA has evaluated and approved its safety and effectiveness for its intended uses
  - FDA drug approval also provides an exclusivity benefit of 6 months to 7 years
- Intended use of the medical product is integral to the FDA oversight process:
  - Likewise, drug applications require description of intended uses and submission of proposed labeling
  - Premarket Approval (PMA) and Premarket Notification (510(k)) require description of intended uses and proof of safety and effectiveness for all such uses
- The safety and effectiveness evaluation by FDA is performed in the context of the intended uses of the product set forth in its proposed labeling:
  - Per FDA internal guidance, in rare cases it might be necessary to infer intended use from other types of information

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## Regulatory Concerns with Off-Label Promotion

- Allowing promotion of off-label uses may encourage companies to minimize the claims in their regulatory applications for easier approval.
- After approval, the company could aggressively market off-label uses for which safety and effectiveness has not been evaluated.
- Little incentive exists for a company to apply for regulatory approval for widely accepted off-label uses:
  - Companies receive the revenue from off-label uses without incurring the cost of studies and regulatory approval.
- During the practice of medicine, a physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA. No rigorous evaluation of safety, effectiveness, or side effects may have been made for the off-label use.

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## FDA Regulation of Off-Label Promotion

- Promotion and advertising by manufacturers for unapproved uses may be punishable as misbranding or adulteration of the medical product.
- Prohibitions against promoting off-label uses are balanced against companies' First Amendment rights to communicate truthful and non-misleading information to doctors and patients.
- FDA's prohibitions against off-label promotion extend only to the manufacturers (and distributors), not to health care practitioners.

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## Off-Label Promotion and Advertising— Reprint Distribution

- The distribution of publication reprints by manufacturers and distributors receives particular regulatory attention.
- FDA has traditionally interpreted the Food, Drug, and Cosmetic Act to give it authority to consider a company's dissemination of reprints of articles about unapproved uses of the company's product as evidence that the company was engaged in illegal marketing.
- Analysis of reprints indicates that some articles do not receive rigorous peer review, that underlying studies lack proper controls or valid sample sizes, and that many articles are actually ghost-written by the product manufacturer or by authors whose financial ties to the manufacturer may impair objectivity.

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## FDA Draft Guidance on Reprints

- Recent draft FDA guidance would have liberalized FDA's position to permit distribution of reprints from peer-reviewed journals that were:
  - Not false or misleading;
  - Not abridged or summarized;
  - Accompanied by approved labeling, a bibliography of other published studies of the unapproved use, and a sample of articles reaching different conclusions;
  - Distributed separately from promotional materials; and
  - Accompanied by certain disclaimers and disclosures.
- Rep. Waxman strongly opposed the draft guidance as "ill-advised" in a November 2007 letter to the FDA and is conducting an inquiry into the guidance. FDA issued the guidance on February 18, 2008, noting that it was being issued in the context of the sunseting of previous reprint regulations in late 2006.

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## FDA Review of Direct-to-Consumer Ads

- The recently passed FDA Amendments Act would have permitted a voluntary review of Direct-to-Consumer (DTC) advertising by the FDA.
- The DTC voluntary advisory review program would have been supported by industry fees (approx. \$40,000 per ad).
- The voluntary review program is currently on hold because Congress did not appropriate funds for it; without appropriations, FDA could not collect the fees.
- The existing requirement to submit ads in advance or at the time of initial publication in accordance with 21 CFR 314.81 remains in effect. FDA reviews such ads and may issue Warning Letters.

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## Off-Label Promotion May Result in False Claim Liability

- Elements of False Claims include:
  - Claim presented to the U.S. Government
  - False or fraudulent
  - Knowledge:
    - Actual knowledge
    - Reckless disregard
  - False claims cases can be brought against entities (e.g., manufacturers) that “cause” the filing of a false claim by a customer

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## False Claims Penalties

- Up to treble damages, PLUS
- \$5,500 to \$11,000 per claim
- Note: Health care providers submit large volumes of claims for medical services each year, so the monetary penalties add up very fast

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## Qui Tam (Whistleblower) Actions

- False Claims Act cases brought by private citizens on behalf of the U.S. government.
- “Qui tam relator” (or “whistleblower”) must be an original source of the information on which the allegations are based.
- The qui tam relator receives 15 to 30 percent of the government’s recovery.
- Almost all fraud and abuse cases involving manufacturers have been brought as False Claims Act whistleblower cases.

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## Qui Tam (Whistleblower) Actions

- “Bootstrapping” theory: In order to provide a basis for a whistleblower case, violations of other laws are alleged to taint claims or cost reports, and render them false:
  - FDA branding, labeling, marketing and promotion restrictions
  - Anti-Kickback Law
  - Stark Law (Physician Self-Referral Law)
- Manufacturers do not file claims, but are accused of causing others to file false claims or of conspiracy to file false claims.

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## New Medicaid False Claims Acts Initiatives

- The Deficit Reduction Omnibus Reconciliation Act of 2005 includes incentives for states to strengthen their own versions of the False Claims Act and increase Medicaid False Claims recovery.
- Cases against InterMune, Warner-Lambert, Serono, and Bristol-Meyers Squibb all included multi-million dollar payments to state Medicaid programs in addition to the federal payments.

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## False Claims Act Theories of Liability Involving Medical Product Companies

- Examples:
  - Consulting fees for undocumented services without a legitimate business purpose
  - Payments in excess of fair market value for research, consulting (including speaker bureaus and speaking honoraria)
  - Selection of consultants based on referrals
  - Scientific advisory board fees (including stock options)
  - “Unrestricted” research or educational grants (not restricted to legitimate research or educational purposes)
  - Purchases of unnecessary clinical research involving company products
  - Purchases of sales data which is publicly available for lower cost
- Involvement of sales and marketing personnel can be viewed as evidence of improper purpose.
- As always, beware of creating e-mail communications that can be used to support False Claim theories.

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## Unfortunately, there are no bright lines because:

- These are state-of-mind crimes.
- Bad intent can negate good intent.
- Corporate intent is collective.
- Bad customer intent can be contagious.
- Intent is not always knowable without hindsight.
- Large settlements allow these theories of liability to gain acceptance without judicial validation.

Note: Industry contends that truthful off-label communication should not support a False Claims Act violation absent evidence of other illegal activity.

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## Off-Label Uses Under Medicare Part D

- Medicare Part D plans may deny coverage for prescriptions for off-label uses, relative to Medicare-referenced drug compendia.
- Peer-reviewed evidence is not allowed in support of off-label uses in Part D, as it is in Part B.
- Medicare Appeals Council is not required to review Part D cases within 90 days, unlike Parts A and B.

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## Recap of Areas for Regulatory Affairs Attention

- Review intended uses in submissions to FDA.
- Review of labeling and labeling changes to ensure that promoted uses have been approved by FDA.
- Review of advertising to ensure that it promotes only approved uses.

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## Conclusions

- Remember!
  - Off-label promotion by manufacturers renders the medical product adulterated or misbranded under the FDCA.
  - Off-label promotions can contribute to other related offenses, most notably False Claims Act liability.
    - False Claims Act penalties can include:
      - \$15,000 per claim
      - Treble damages
      - Jail time

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