

Detecting Off-Label Promotion Issues That Can Derail a Life Sciences M&A



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Importance of Off-Label Due Diligence in Life Sciences M&A

- Off-label sales are often an important revenue source for the target product or company
- Continued focus on off-label promotion in government investigations for both pharmaceuticals and medical devices
- Pending healthcare reform legislation likely to further enhance enforcement focus
- Potential for acquisition of significant liability by the acquiring company

Examples of Government Health Care Fraud Settlements With Life Sciences Companies

YEAR	COMPANY	SETTLEMENT
2009*	Eli Lilly	\$1.4 billion settlement to resolve off-label marketing of <i>Zyprexa</i> . The sum includes a \$515 million criminal fine and an \$800 million civil settlement with the federal government and states. Approximately \$362 million is to be paid to the states for Medicaid claims.
2008	Cephalon	\$425 million settlement with the U.S. DOJ to resolve allegations of off-label promotion of <i>Atiq</i> , <i>Gabitril</i> , and <i>Provigil</i> ; \$375 million of sum goes to federal and state Medicaid and other health care programs.
2007	Bristol-Myers-Squibb	\$500 million settlement with federal government, 44 states and DC over alleged illegal marketing and pricing of <i>Abilify</i> , <i>Serzone</i> and other drugs; approximately \$187 million went to states for Medicaid restitution
2006	Schering- Plough	\$435 million national settlement over allegations of underpayment of Medicaid rebates for Claritin, off-label marketing of <i>Temodar</i> and illegal inducements to physicians to prescribe <i>PEG-Intron</i> , <i>Rebetron</i> and <i>Intron-A</i> . Of this amount, 49 states and DC received \$203 million in Medicaid recovery.
2005	Serono	\$704 million settlement with federal government and 42 states and DC over marketing of HIV wasting drug <i>Serostim</i> and other violations; \$262 million went to Medicaid Fraud control Units.
2004	Warner-Lambert/Pfizer	\$430 million settlement with federal government and 50 states and DC to resolve allegations of <i>Neurontin</i> off-label marketing; approximately \$40 million went to states for violation of consumer protection laws and \$68 million for Medicaid restitution.
2003	AstraZeneca	\$354.9 million settlement with federal government state Medicaid programs over <i>Zoladex</i> marketing practices; \$24.9 million went to states.

* Eclipsing the Eli Lilly fine, is the pending Pfizer settlement of \$2.3 billion related to alleged off-label marketing of the now withdrawn painkiller *Bextra*. The settlement requires approval of a federal judge, and would be the largest ever paid by a drug company to resolve alleged marketing violations.

Examples of Alleged Off-Label Actions Cited in Settlements

DATE	COMPANY	PRODUCT	ALLEGED OFF-LABEL ACTIONS
Sept. 2007	Bristol-Myers Squibb	<i>Abilify</i>	Promoted the sale of the drug for pediatric use and dementia-related psychosis, both off-label uses.
July 2007	Jazz Pharmaceuticals	<i>Xyrem</i>	Made sales calls to physicians, who did not specialize in the area that the drug was approved for, and promoted the drug for off-label treatments and distributed off-label promotional materials. Paid a psychiatrist to give talks around the country to promote the drug for off-label uses.
May 2007	The Purdue Frederick Company	<i>OxyContin</i>	Promoted the drug as less addictive, less subject to abuse, and less likely to cause withdrawal symptoms than other pain medications without FDA approval.
May 2007	Medicis	<i>Loprox</i>	Targeted pediatricians and urged them to use the drug as a treatment for diaper rash—the drug is approved as a fungicide and not for treating children under 10 years of age.
Apr. 2007	Cell Therapeutics, Inc.	<i>Trisenox</i>	Falsely marketed to physicians by suggesting that it was FDA approved for treating a different type of cancer than approved for, and was listed as medically accepted in the compendia for treating other types of cancers. Used illegal kickbacks to induce physicians to prescribe the drug and paid them to attend dinners or conferences on off-label uses.
Apr. 2007	Pfizer	<i>Genotropin</i>	Promoted drug for off-label uses, such as anti-aging, cosmetic use, and athletic performance enhancement.

Examples of Alleged Off-Label Actions Cited in Settlements (cont'd)

DATE	COMPANY	PRODUCT	OFF-LABEL ALLEGATIONS
Oct. 2006	InterMune, Inc.	<i>Actimmune</i>	Conducted a clinical trial, which failed to establish statistically significant evidence of benefit, but published press releases indicating false outcomes from the clinical trials. Conducted sales of the drug from August 2002 through January 2003 that were attributable to the prescribing of the drug for the treatment of Idiopathic Pulmonary Fibrosis, an off-label use.
Aug. 2006	Schering-Plough	<i>Temodar and Intron A</i>	Conspired to make false statements to FDA regarding its improper promotional activity in response to FDA's inquiry regarding certain illegal promotional activities by the company's sales representatives at a national medical conference for oncologists. These false statements were designed to reassure FDA that the promotional activities were isolated and not directed by the home office, when they were actually widespread and part of the national marketing plan.
Oct. 2005	Serono, S.A.	<i>Serostim</i>	Conspired with a medical device manufacturer to market computer software packages to diagnose AIDS-wasting, although the device was not approved by FDA for this use. The drug company then tried to increase the market for such devices in order to increase the market for the drug. Offered physicians all-expense paid trip to encourage off-label prescriptions.
Dec. 2005	Eli Lilly	<i>Evista</i>	Trained sales representatives to prompt or bait questions by physicians to promote the drug for off-label uses. Encouraged sales representatives to send medical letters and other marketing materials that were not requested by physicians in order to promote off-label uses.
May 2004	Pfizer	<i>Neurontin</i>	Encouraged sales representatives to provide one-on-one sales pitches to physicians about off-label uses. Sponsored "independent medical education" events on off-label uses and misled the medical community on the content and lack of independence.

Digging Deeper: Key Indicators of Potential Off-Label Promotion Issues

- Key areas of review to identify potential off-label promotion issues:
 - Corporate Compliance Program
 - Knowledge of Industry Standards for Marketing and Promotion
 - Training and Training Protocols
 - Staff Retention History
 - Policies and Procedures Regarding Interactions with Medical Personnel
 - Promotional Materials and Practices
 - Scientific Literature/Reprints
 - Grants/Payments to Healthcare Providers and Organizations
 - Sponsorship of Meetings and Conferences (CME)
 - Litigation/Investigation/Compliance History and Collaborations

1. *Weak or Non-existent Corporate Compliance Program*

- Does target have a state-of-the-art compliance program, designed to detect illegal practices, including off-label violations?
 - *E.g., Anonymous hotlines; open-door communication policies; routine use of internal audits; up-to-date recordkeeping and reporting practices; annual review of procedures - especially those concerning promotional materials and activity; prompt and proactive corrective action when problems detected; and other compliance controls*
- Does it address compliance with applicable statutory and regulatory authorities?
 - *E.g., Federal Food, Drug, and Cosmetic Act; Public Health Service Act; Anti-kickback Statute; False Claims Act (federal & state); state marketing disclosure laws*
- Does the target have a corporate integrity agreement (CIA)?

2. Lack of Knowledge of Industry Standards for Marketing and Promotion

- Does the target have procedures to familiarize its staff with applicable industry promotional guidance?
 - **OIG Compliance Program Guidance for Pharmaceutical Manufacturers**
 - **FDA regulations and guidance documents on promotion and marketing**
 - **PhRMA Code on Interactions with Healthcare Professionals**
 - **PhRMA Guiding Principles of DTC Advertising**
 - **AdvaMed Code of Ethics on Interactions with Health Care Professionals**
 - **AMA Guidance on Interactions with Pharmaceutical Industry Representatives**
 - **ACCME Standards for Commercial Support**

3. Inadequate Training and Training Protocols

- Who receives training?
 - Sales representatives
 - Medical science liaisons (“MSLs”)
 - Marketing managers/executives
- Content of training?
 - Are off-label violations well-addressed?
 - Are staff trained or instructed in any way concerning off-label properties (safety profile/efficacy)? Off-label target populations? Off-label patterns of treatment?
 - For medical devices, is there training of technical support personnel regarding off-label promotion?
- How frequently are staff being retrained?
 - Annually, or not at all?
- Is there ongoing monitoring of personnel?
- Quality of trainers and training materials?

4. Staff Retention History

- Has the target experienced substantial resignations or terminations?
 - Former employees who left target may have direct knowledge of off-label promotion practices → potential *qui tam* or “whistleblower” plaintiffs
 - Have senior executives or sales force personnel left recently?
 - Evaluate whether former officials/sales reps should be interviewed by an investigative firm

5. Formal (and Informal) Policies and Procedures Regarding Proper Interactions with Medical Personnel / Buyers

- Are policies and procedures for sales and marketing written, comprehensive, and up-to-date?
- Do they identify and address off-label promotion?
- Do they communicate clearly and unambiguously what detail force can and cannot do regarding marketing / promotion?

6. *Form and Substance of Promotional Materials and Practices*

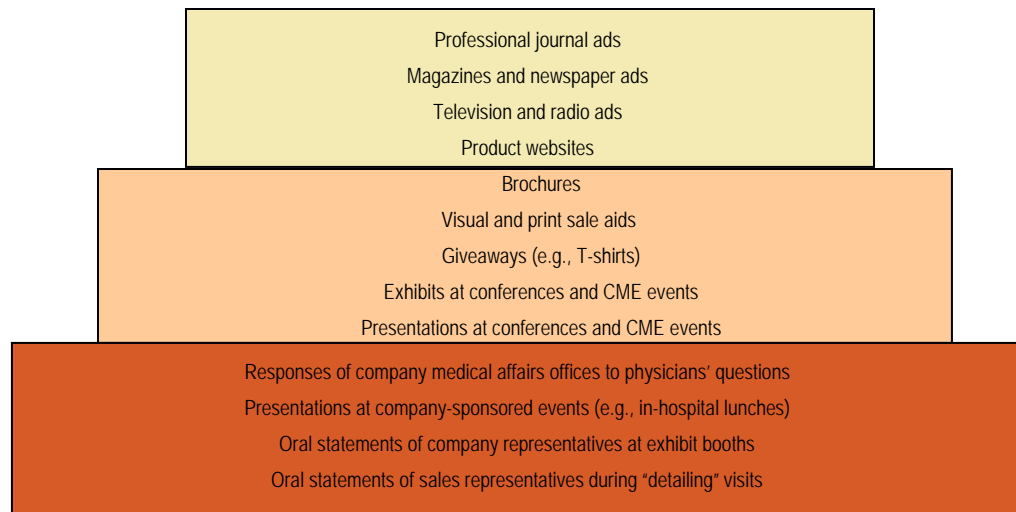
- Are target's promotional materials consistent with FDA (and FTC where applicable) requirements?
 - Review formal and informal promotional materials produced by target and sales reps
 - Review print and electronic media ads, including Internet sites
 - Review any social media activities (Facebook, LinkedIn, YouTube, Twitter, MySpace, "sponsored post" blogs)
 - Note new FDA Draft Guidance on Risk Communication in Prescription Drug and Device Promotion (May 29, 2009)
- Are target's promotional materials subject to periodic review? Is compliance audited?
- Is sales/marketing staff and/or sales reps incentive compensation related in any way to levels of off-label sales
 - Is there any perception by marketing staff/sales reps that the target's management is expecting or encouraging them to focus on off-label sales

Detectability of Types of Off-Label Promotion of Pharmaceuticals

Highest



Lowest



FDA Citations of Off-Label Violations

Frequency of Violations in 117 Regulatory Letters, Calendar Years 2003-2007

Cited violation	Number of regulatory letters	Percentage of total letters*
1. Omission or minimization of risk	95	81
2. Overstated effectiveness or unsubstantiated effectiveness claims	54	46
3. Off-label promotion	42	36
4. Unsubstantiated superiority or comparative claims	40	34
5. Failure to submit required material to FDA	18	15
6. Other	27	23

* Percentages do not add to 100 because most letters cite more than one violation.

7. Scientific Literature / Reprints

- Does scientific and medical information disseminated by the target comply with new FDA Good Reprint Practices Guidance (Feb. 2009)?
 - E.g., reprints should be on unapproved uses of approved or cleared drugs and devices, unabridged, peer-reviewed, generally available in textbooks, not be false or misleading, not pose a significant risk to public health if relied on, distributed separately from promotional information, not edited or influenced or primarily distributed by the manufacturer
 - Are adequate disclosures provided, e.g., of any authors known to the target that have a financial interest in or are receiving compensation from the target, the authors' affiliations, the non-approved status of the indication and the manufacturer's interest in the drug or device?
 - Are all significant risks known to the target concerning the unapproved product disclosed, approved labeling and comprehensive bibliography provided, and articles with contrary conclusions supplied?

8. Grants to Healthcare Providers, Managed Care Organizations, Academic Institutions

- Could target's financial support of research and education grants be construed as an induce-ment to prescribe or promote a product for an off-label use?
- Do the target's grants comply with applicable OIG requirements?
 - **Is compliance audited?**
- Note ACCME Standards for Commercial Support

9. Target's Sponsorship of CME Events, Conferences, and Professional Meetings

- Could programs be viewed as not “independent” of the target’s influence?
- Could the target’s support of educational programs be viewed as promotional, rather than legitimate scientific exchange?
- Does content of meetings have a significant or exclusive focus on off-label uses?
- E.g., federal and 17 states’ action against Amgen, AmerisourceBergen, and Wyeth alleging unlawful off-label promotion through CME programs presented on Medscape (filed Feb. 27, 2009)
- FDA Guidance on Industry-Supported Scientific and Educational Activities (1997)

10. *Litigation/Investigation/Compliance History and Collaborations*

- Government Investigations
 - Any pending FDA, OIG, or state investigations/complaints related to off-label promotion?
 - Any debarred individuals or entities?
- Any pending private actions
- Settlements
 - Any recent settlements or judgments in private actions or with DOJ and/or states regarding off-label promotion?
 - Any corporate integrity agreements (CIAs) or other settlement restrictions?
- Collaborations
 - Does the target use sales reps from contract sales organizations or in alliance with other drug or device manufacturers? What coordination or compliance arrangements, or liability agreements, are in place?
 - Will the collaborations accompany acquisition of the product or company?

Practical Difficulties in Off-Label Due Diligence

- Dealing with time constraints – focusing the review
 - Limiting review of documents to e-data room and review of FDA website regarding Warning Letters / other actions on promotions
 - Limiting interviews of individuals to target's senior marketing and medical officials
 - Limiting outside reviews to research on complaints / concerns regarding off-label promotion (e.g., cafepharma.com message board)

Practical Difficulties in Off-Label Due Diligence (Con't)

- Maintaining secrecy when a deal is not public
 - Assess possibility and degree of adequacy of due diligence in view of limitations on direct access to company officials / sales force
 - Assess possibility and degree of adequacy of due diligence in view of limitations on scope of internal target documents available
 - Assess desirability of using an investigative firm to obtain information concerning market practices, reputation, training, and compliance reputation from recent former officials and sales reps of the target

Practical Difficulties in Off-Label Due Diligence (Con't)

- Quantifying risks
 - Scope and degree of off-label promotion concerns identified
 - Scope and potential liability from any pending private complaints or government investigations or actions
 - Potential for retention of possible liabilities by target's owners
 - Degree to which valuation of product or target may be affected by potential changes in product coverage or reimbursement for off-label uses of drugs or devices by the Centers for Medicare and Medicaid Services (CMS), other government purchasers (VA, DOD), or private insurers
 - Degree to which potential for and magnitude of FDA/OIG/DOJ/private challenges to off-label promotion by the target can be predicted
 - Assessment of how off-label sales are reflected in the acquisition price

Appendix: Model Due Diligence Checklist for Off-Label Promotion Issues

- Assemble experienced due diligence team
 - E.g., lawyers, regulatory scientists, and other subject matter experts
- Develop a strategy for approaching due diligence within applicable timeframes, focusing on:
 - Products – investigational and marketed
 - Operations – promotion, marketing, and distribution
- Develop information on target from publicly available sources
 - Public statements by target
 - Annual reports
 - Filings and other correspondence with regulatory agencies contained in publicly accessible electronic databases

Appendix: Model Due Diligence Checklist (cont'd)

- Use of E-data/virtual room
 - Draft and provide document requests to target
 - Conduct comprehensive review of pertinent documents, reports, and filings
 - Send targeted inquiries regarding company's marketing and promotion practices
- Interview management and senior executives, sales reps, and MSLS concerning marketing and promotion practices and history
- Review current sales/marketing materials
- Review sales force and MSLS training materials
- Review field practices

Appendix: Model Due Diligence Checklist (cont'd)

- Review pending and approved marketing applications, and correspondence, for all FDA-regulated products
 - New Drug Applications (“NDA”)
 - Abbreviated New Drug Applications (“ANDA”)
 - Supplemental New Drug Applications (“SNDA”)
 - Biologics License Applications (“BLA”)
 - Pre-Market Approval Applications (“PMA”)
 - 510(k) device marketing clearances
- Review final labeling for all products approved by FDA and any proposed labeling for products in the pipeline
 - Identify any inconsistencies in approved labeling and marketing/promotion materials

Appendix: Model Due Diligence Checklist (cont'd)

- Review target's promotional and marketing materials, press releases, brochures, abstracts, published studies, print and electronic ads, social media activities, and any other relevant statements for all FDA-approved or cleared drugs and devices
 - Determine if there are any false or misleading representations
 - Assess support of scientific studies for promotional activity
 - Inquire about ghost-writing of journal articles
 - Inquire about marketing ruses such as "seeding trials"
- Review all correspondence between target and regulatory agencies relating to off-label concerns and noting how issues have been resolved
 - Warning Letters
 - Untitled Letters
 - Cyber Letters
 - DDMAC communications
 - FTC communications
 - Trade complaints (with, e.g., FDA, FTC, or NAD)

Appendix: Model Due Diligence Checklist (cont'd)

- Review reports of internal audits, meeting minutes, and other recordkeeping regarding marketing / promotion
 - How has target reacted when it became aware of off-label promotion allegations or reports
 - Did response follow stated policies and procedures
 - Any evidence that consideration was given by the target to conducting clinical trials for off-label indications to determine safety and efficacy
- Compliance with FDA/OIG requirements and guidances and with any CIAs and settlements
- Determine whether company has ever (or is being) investigated by FDA, OIG, DOJ, or other governmental entities for off-label promotion. If so, obtain relevant documentation related thereto. Sources of information, other than target, include:
 - Internet
 - FDA, DOJ, OIG
 - Industry news
 - Pharma and device industry blogs and message boards
 - Trade and general press
 - Private Investigative firm

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