

Contradictory Actions on Off-Label Use of Prescription Drugs? The FDA and CMS Versus the U.S. Justice Department

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On January 15, 2009, the U.S. Justice Department posted a notice on its website that Eli Lilly and Company had agreed to pay a criminal fine of \$515 million, the largest such fine ever paid in a health care case, to resolve allegations that the company had promoted olanzapine (Zyprexa) for uses not approved by the U.S. Food and Drug Administration (FDA).¹ The indications approved by the FDA for olanzapine include (a) schizophrenia, (b) bipolar disorder, and (c) agitation associated with schizophrenia and bipolar I mania.² In the plea agreement, Eli Lilly admitted that it promoted olanzapine for “off-label” uses such as treatment of dementia. In addition to the \$515 million criminal fine, Eli Lilly agreed to forfeit assets of \$100 million and to pay up to \$800 million to compensate states and the federal government for “false claims” paid by Medicaid, TRICARE, and the Federal Employee Health Benefits Program; drug coverage in these programs is restricted to use for FDA-approved indications. The federal government will receive 55% of the \$800 million civil fine, and up to \$361 million will be paid to the states that participate in the agreement negotiated by the U.S. Justice Department. The \$800 million civil fine resolves 4 *qui tam* (false claim) motions, all filed by former Lilly sales representatives.

Less than 2 weeks later, on January 26, 2009, Pfizer agreed to a settlement for the off-label promotion of valdecoxib (Bextra) that eclipsed the size of previous settlements.^{3,4} The proposed settlement for \$2.3 billion made the \$430 million settlement paid by Pfizer in 2004 (on behalf of Warner-Lambert) for the off-label promotion of gabapentin (Neurontin) look small.⁵ And, there appear to be more settlements in process between pharmaceutical manufacturers and the U.S. Justice Department. In early February 2009, GlaxoSmithKline warned that its earnings in 2008 would be affected by a \$400 million legal charge related to the 5-year-old federal investigation into “marketing and promotional practices for several products for the period 1997 to 2004.”⁶

The notice from the U.S. Department of Justice of the \$1.415 billion that Eli Lilly will pay for the off-label promotion of olanzapine included a quote from the Special Agent-in-Charge of the Defense Criminal Investigative Service: “The illegal scheme used by Eli Lilly significantly impacted the integrity of TRICARE, the Department of Defense’s healthcare system. This illegal activity increases patients’ costs, threatens their safety and negatively affects the delivery of healthcare services to the over nine million military members, retirees and their families who rely on this system. Today’s charges and settlement demonstrate the ongoing commitment of the Defense Criminal Investigative Service and its partners in law enforcement to investigate and prosecute those that abuse the government’s healthcare pro-

grams at the expense of the taxpayers and patients.”¹

Yet, during the same month, another federal agency offered a seemingly different approach to off-label use of prescription drugs when the FDA relaxed rules for off-label promotion by manufacturers to physicians and other entities. The FDA’s action followed a decision made 2 months earlier, in November 2008, by the Centers for Medicare and Medicaid Services (CMS) that expanded Medicare coverage to include off-label uses of chemotherapy drugs. These apparently discrepant actions by 3 federal agencies are not as disjointed as they might initially appear.

FDA Permits Off-Label Promotion to Physicians

The FDA formalized in January 2009⁷ the draft guidance released last year that proposed relaxation of rules on the promotion of off-label uses of drugs to physicians, other health care professionals and entities such as health plans and pharmacy benefit managers.⁸ In the current FDA guidance, manufacturers can promote the off-label uses of prescription drugs despite (a) the preference by the FDA that manufacturers seek formal approval for all promoted indications, and (b) concern that approved labeling does not provide “adequate directions for use” for unapproved (unlabeled) indications. Specifically, the current FDA guidance permits manufacturers to disseminate “truthful and non-misleading medical and scientific information on unapproved uses of approved or cleared medical products” contained in published literature if “Good Reprint Practices” are followed.

The definitions of good reprint practices and what constitutes acceptable material are lengthy.⁷ Specifically cited as unacceptable are letters to the editor, article abstracts, reports of Phase 1 trials in healthy subjects, and “reference publications that contain little or no substantive discussion of the relevant investigation or data.” Publications funded by manufacturers or that were “edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer” are also deemed unacceptable. Other definitions of materials that would not meet good reprint practices include information that is “false or misleading” or that would “pose a significant risk to the public health, if relied upon.” Of course, what constitutes false or misleading information or poses a risk to public health is open to interpretation, relying on “the weight of credible evidence derived from adequate and well-controlled clinical investigations.” A line in the sand is drawn for the exclusion from good reprint practices of discussion of “a clinical investigation where FDA has previously informed the

company that the clinical investigation is not adequate and well-controlled.” The FDA guidance also relies heavily on peer review and publication “in accordance with the peer-review procedures of the [publisher of the journal].”⁷

Peer Review Does Not Ensure Quality of Evidence

The medical literature landscape is riddled with instances of breaches of integrity, including the influence of the pharmaceutical industry in ghost writing,^{9,10} ghost management,¹¹ publication planning,¹² and more recently the discovery of the conduct of “seeding trials.”¹³ Following the release of the FDA draft guidance on good reprint practices last year, Psaty and Ray criticized the wisdom of the FDA draft guidance, describing 4 specific problem areas:¹⁴

1. *Selective publication of studies*: makes the peer-reviewed literature an incomplete and inaccurate summary of the total knowledge about a particular product—such as the recent description (Turner et al. 2008)¹⁵ of selective publication of positive clinical trials with antidepressants.
2. *Manipulation of the literature*: includes evidence of ghost authorship in much of the published literature, as well as ghost management and publication planning.^{9-12,16}
3. *Absence of critical information*: ghost management and selective publication result in an absence of critical and unfavorable information; e.g., use of hormone replacement therapy for preventing coronary heart disease without evidence from randomized controlled trials.
4. *Potential for undermining the New Drug Application (NDA) review process*: inadequate supervision of off-label use could encourage NDAs for the easiest indication and avoid performing clinical trials that would better define the risk-benefit profile of the drug.

CMS Expands Medicare Coverage of Chemotherapy Drugs for Off-Label Uses

A third federal agency adds additional flavor to the brew of off-label prescription drug use in the United States. In November 2008, CMS quietly expanded Medicare coverage of chemotherapy drugs to include many off-label uses,¹⁷ despite evidence from a technology assessment performed by the Agency for Healthcare Research and Quality (AHRQ, May 2007) that found a general lack of agreement among 6 compendia, including the 4 presently used by CMS, regarding recommendations for use of particular chemotherapy drugs for specific indications.¹⁸ CMS also canceled a cost analysis of the effect on Medicare spending from this expansion in coverage, which will now add an unknown amount to spending that totaled \$2.7 billion for chemotherapy drugs in 2007. An investigative report found that the expansion in Medicare coverage will be a boon for manufacturers such as Eli Lilly and its chemotherapy drug gemcitabine (Gemzar), which has label indications for 4 types of cancer, but is used off-label for many more types of cancer such as advanced cervical cancer, despite “inconclusive” evidence that gemcitabine is effective for this type of cancer.¹⁹

Gemcitabine costs between \$2,500 and \$5,000 per month.

More specific implications for Medicare spending that result from this expansion in coverage can be derived from other examples. Bevacizumab (Avastin) from Genentech is not approved for use in ovarian cancer, and Medicare rejected nearly all of an estimated \$16 million in requests from physician offices in 2007 for coverage in treatment of women with ovarian cancer.¹⁹ Because bevacizumab has only weak evidence of efficacy in ovarian cancer and has been associated with gastrointestinal perforation,^{20,21} these coverage exclusions by Medicare intermediaries in 2007 seem effective in controlling more than drug costs.

Current CMS policy on “medically-accepted” off-label use of chemotherapy drugs for Medicare beneficiaries relies on 4 compendia. The 140-page AHRQ technology assessment released in May 2007 evaluated 6 compendia including the 4 currently used by Medicare intermediaries to make coverage decisions.¹⁸ For the 14 specific off-label cancer-agent indications studied, each indication was mentioned by at least 1 of the 4 compendia used in Medicare decisions, and the use was often not identified as off-label. For example, the National Comprehensive Cancer Network (NCCN) compendia does not indicate if the mentioned use is off-label, such as the use of bevacizumab for breast and lung cancer (the drug is approved for colorectal cancer only). The AHRQ technology assessment also found that when an off-label use was not mentioned in the compendia, it was not possible to determine whether or not the silence was attributable to evaluation of evidence. Other criticism included lack of transparency in methods, and “evidence rating schemes and editorial policies that would allow a non-approved indication that can be qualified as equivocal” for NCCN and the American Hospital Formulary Service-Drug Information (AHFS-DI);¹⁸ both compendia are used currently in Medicare coverage decisions. Investigative reporters found that NCCN comprises 21 well-recognized cancer centers that employ experts who have financial ties to manufacturers of chemotherapy drugs.¹⁹ Since 2008, The American Hospital Formulary Service compendium, published by the nonprofit American Society of Health-System Pharmacists, has had a financial relationship with a foundation that charges a \$50,000 fee to the manufacturer to have new uses of a drug reviewed.¹⁹

There may be a reasonable argument that some off-label use of chemotherapy drugs is warranted because there is sufficient evidence to support use in certain conditions that have not received FDA approval. As the AHRQ technology assessment observes, research advances can “outpace approval rates by the FDA,” and there may be no FDA-approved drug for rare cancers.¹⁸ On the other hand, evidence is continually emerging, and investigators continue to be surprised by chemotherapy regimens that do not produce the anticipated benefit in survival, progression-free survival, or quality of life.²² In their February 2009 report of the results of a randomized trial of 755 patients with previously untreated metastatic colorectal cancer, Tol et al. found that the addition of cetuximab to a combination of capecitabine, oxaliplatin, and bevacizumab was associated with shorter progression-free survival (9.4 months) compared with 10.7 months ($P=0.001$)

in the group that received the 3-drug combination without cetuximab.²³ The addition of cetuximab also had no effect on overall survival or treatment response and was associated with a higher rate of serious adverse events and lower quality of life compared with the 3-drug regimen. An editorialist commented that these results “underscore the fundamental importance of subjecting hypotheses to carefully conducted clinical trials.”²²

The benefits of trial and error with chemotherapy drugs in new (off-label) indications should be carefully weighed against the potentially high costs—both the dollar cost of the chemotherapy drugs and the risk of adverse events. CMS may not be followed by a stampede of private insurers in its decision to open the federal government’s wallet for spending on off-label chemotherapy drugs, although Bach noted recently that 32 states, accounting for about 74% of the U.S. population, have some type of mandate for coverage of off-label use of chemotherapy drugs by private payers.²⁴

Among the strategies employed by CMS to control utilization and spending on drugs and medical services, limiting coverage (by therapeutic indication) may be the most successful method. For example, Bach points out that in 2007 CMS restricted coverage of erythropoiesis-stimulating agents (ESA), both with respect to the type of patient and clinical scenario in which ESAs could be used, resulting in an estimate by the manufacturer of the ESA darbepoietin (Aranesp) that its annual sales for Medicare patients would drop by 80% to \$200 million from \$1 billion.²⁴ Notably, the 2007 CMS decision was based on “emerging safety concerns.”²⁵ In November 2007, the FDA issued a Public Health Advisory to “patients with cancer,” stating that use of ESAs “may shorten your survival time or may cause your tumors to grow faster,” should be used only to treat anemia associated with chemotherapy, and “should be stopped after you complete your course of chemotherapy.”²⁶ ESAs are the subject of an ongoing safety investigation by the FDA.²⁷

Off-Label Promotion Can Be a Good Thing or a Bad Thing

Permitting the promotion of drugs for off-label uses may be appropriate in instances in which a drug can improve quality (e.g., same or better outcomes at lower cost). For example, Stafford noted previously that off-label uses of drugs sometimes make their way into “evidence-based guidelines,” such as first-line therapy with gabapentin for (painful) diabetic peripheral neuropathy or the use of aspirin in diabetes for the prevention of cardiovascular events.²⁸ However, the ability of physicians to prescribe drugs for off-label uses can allow a drug manufacturer to forego the expense of conducting rigorous clinical trials and instead “game” the system by obtaining FDA approval for an achievable secondary indication and then promote the drug for an unapproved use. Stafford argues that allowing pharmaceutical manufacturers to step-up such promotion by distributing published medical literature to physicians is not in the public’s best interest in part because the industry-sponsored trials of drugs for off-label uses are “too often of limited quality, industry-sponsored, and placebo-controlled (rather than comparisons

with approved therapies).” Stafford in his commentary also notes that the guidelines “nearly nullify themselves by emphasizing their nonbinding nature, they also suggest a more permissive attitude toward the promotion of off-label uses of drugs.”²⁸ Since aspirin and generic gabapentin are inexpensive and effective for their off-label uses in accepted treatment guidelines, patients and the health care system benefit from improved quality (efficiency) of care. However, these instances of apparently desirable promotion of drugs for off-label use generally pertain to generic drugs for which there is no commercial interest.

Perhaps more clear are the effects of advocacy of off-label use of expensive brand drugs. For example, a review published in a peer-reviewed journal in March 2008 advocated the use of 2 expensive drugs for diabetic peripheral neuropathy: duloxetine (Cymbalta) and pregabalin (Lyrica).²⁹ This review dismissed inexpensive generic gabapentin for this use due to “limited data on its efficacy” which “may preclude its use as a first-line agent,” thereby ignoring the role of gabapentin as first-line therapy for diabetic peripheral neuropathy in treatment guidelines.^{28,30,31} A recent systematic review performed by the Canadian Agency for Drugs and Technologies in Health found that duloxetine and venlafaxine were inferior to tricyclic antidepressants (TCAs) and anticonvulsants (e.g., gabapentin) in clinical response in patients with neuropathic pain.³² Yet, in analysis of societal (all payer, direct and indirect) cost per patient, duloxetine cost 63% more than TCAs and 31% more than anticonvulsants.³²

Pharmaceutical manufacturers are expert at conducting effective promotional campaigns, and the behavior that results from these commercial endeavors can adversely affect quality of care. As part of its comparative effectiveness research, AHRQ concluded in 2007 that there was “insufficient high-grade evidence to reach conclusions about the efficacy” of atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) for off-label uses such as dementia, severe geriatric agitation, depression, obsessive-compulsive disorder, autism, Tourette’s syndrome, posttraumatic stress disorder, and personality disorders.³³ In the debate about the First Amendment rights of pharmaceutical manufacturers,³⁴ Kesselheim and Avorn remind us that the Kefauver-Harris Drug Amendments of 1962 gave the FDA additional authority to regulate the advertisement of prescription drugs, and these authors suggest that this authority could be helpful in countering marketing campaigns that might not be in the public’s best interest.³⁵ For example, the heavy promotion of calcium channel blockers in the 1990s resulted in these drugs becoming the most common agents for treating hypertension even though they are not first-line therapy for most patients.

Off-Label Promotion Is Effective

The details of drug manufacturer promotion of drugs for off-label uses have come into the public’s consciousness as a result of the discovery process in litigation and government investigations.³⁶ The whistle-blower lawsuit that broke new ground in allegations about promotion of off-label uses of gabapentin was filed in 1996 in the U.S. District Court in Boston but was not unsealed until

March 2002.³⁷ In that case, which led to the \$430 million settlement paid by Pfizer, court documents showed that about half of physicians surveyed between October 1995 and December 1998 said they had received marketing appeals from the company's sales representatives on unapproved uses;³⁸ the off-label use of gabapentin for pain rose from 1% in 1995 to 41% of use of the drug in 2000.³⁹ Radley et al. found that all off-label uses accounted for 83% of gabapentin utilization in 2001, and 80% of this off-label use had little or no scientific support.⁴⁰

We also know from the public announcement by the U.S. Department of Justice in January 2009 that the \$1.415 billion paid by Eli Lilly was related to the promotion of olanzapine for off-label use for several common conditions such as dementia, agitation, aggression, depression, and generalized sleep disorders.¹ Documents in the criminal investigation contained evidence that the company began its promotion of olanzapine for off-label uses by encouraging physicians treating patients in nursing homes and assisted care facilities to prescribe olanzapine for a side effect of the drug. Company sales representatives were trained to promote the sedation side effect as a "therapeutic benefit, not an adverse event," using the slogan "5 at 5," to refer to 5 mg of olanzapine at 5 PM to help patients sleep.⁴¹

Documents in the \$1.415 billion settlement with the U.S. Justice Department showed that the company expanded its "illegal" marketing strategy to primary care physicians in 2000 with the "Viva Zyprexa" campaign, which had the goal to expand the use of olanzapine into primary care even though the approved indications (schizophrenia and bipolar disorder) are not typically managed by primary care physicians. The announcement by the Justice Department in January 2009 also cited increased risk of adverse effects associated with olanzapine, including significant weight gain, obesity, hyperglycemia, and diabetes,⁴¹ which may have contributed to the apparent zealous pursuit of the case and the admission of guilt by Eli Lilly of "misbranding" olanzapine. Company sales representatives apparently went so far as to promote the weight gain of olanzapine as a therapeutic benefit for patients who had trouble maintaining their weight. Gregory G. Katsas, the assistant attorney general for the civil division of the Department of Justice said, "Off-label promotion of pharmaceutical drugs is a serious crime because it undermines the FDA's role in protecting the American public by determining a drug is safe and effective for a particular use before it is marketed."¹

If the off-label promotion of prescription drugs is a "serious crime," how does one interpret the actions by the FDA to expand permissible off-label promotion and by CMS to pay for chemotherapy drugs for off-label use based on recommendations from sources that are influenced by the manufacturers of the chemotherapy drugs? While these actions by the U.S. Justice Department, FDA, and CMS seem to be in conflict, perhaps timing is everything. However, the situation is not as simple as saying that what was unlawful yesterday is lawful today.

We eagerly await better evidence about the effect of promotion of off-label drug use on health care cost and quality. Until then,

perhaps we can take solace in the details of the FDA guidance, such as the suggestion that "scientific or medical information" about off-label use "be disseminated with a representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use."⁷ Seems like a lot of surveillance may be in store, but an "innocent until proven guilty" approach is suggested by this statement in the summary: "FDA does not intend to consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as establishing *intent* [emphasis added] that the product be used for an unapproved new use."⁷

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REFERENCES

1. U.S. Department of Justice. Eli Lilly and Company agrees to pay \$1.415 billion to resolve allegations of off-label promotion of Zyprexa. No. 09-038. January 15, 2009. Available at: <http://www.usdoj.gov/opa/pr/2009/January/09-civ-038.html>. Accessed February 3, 2009.
2. U.S. Food and Drug Administration. Zyprexa product label and approval history. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=ZYPREXA>. (Search on "Zyprexa"). Accessed February 3, 2009.
3. Edwards J. How Pfizer hid a \$2.3 bill. Bextra settlement in plain sight. BNet. January 26, 2009. Available at: <http://industry.bnet.com/pharma/1000656/how-pfizer-hid-a-23-bill-bextra-settlement-in-plain-sight/>. Accessed February 7, 2009.
4. Winslow R. Pfizer sets \$2.3 billion settlement – agreement with U.S. tied to alleged off-label marketing of painkiller Bextra. *Wall Street J*. January 27, 2009. Available at: http://online.wsj.com/article/SB123301757444517869.html?mod=rss_Health. Accessed February 9, 2009.
5. U.S. Department of Justice. Warner-Lambert to pay \$430 million to resolve criminal & civil health care liability relating to off-label promotion. No. 04-322. May 13, 2004. Available at: http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm. Accessed February 7, 2009.
6. Whalen J. Glaxo warns of charge, hints at pact. *Wall Street J*. January 30, 2009:B3. Available at: http://online.wsj.com/article/SB123327051846730799.html?mod=todays_us_marketplace. Accessed February 9, 2009.
7. U.S. Food and Drug Administration. Guidance for industry – good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices U.S. January 2009. Available at: <http://www.fda.gov/oc/op/goodreprint.html>. Accessed February 7, 2009.

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8. U.S. Food and Drug Administration. FDA proposes guidance for dissemination of information on unapproved uses of medical products – agency accepting public comments for 60 days. February 15, 2008. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01798.html>. Accessed February 7, 2009.
9. DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science – the adverse effects of industry influence. *JAMA*. 2008;299(15):1833-35.
10. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib. A case study of industry documents from rofecoxib litigation. *JAMA*. 2008;299(15):1800-12.
11. Sismondo S. Ghost management: how much of the medical literature is shaped behind the scenes by the pharmaceutical industry? *PLoS Med*. 2007;4(9):1429-33. Available at: http://medicine.plosjournals.org/archive/1549-1676/4/9/pdf/10.1371_journal.pmed.0040286-L.pdf. Accessed February 7, 2009.
12. Steinman MA, Bero L, Chren M, Landefeld C. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. 2006;145(4):284-93. Available at: <http://www.annals.org/cgi/reprint/145/4/284.pdf>. Accessed February 7, 2009.
13. Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med*. 2008;149:251-58.
14. Psaty BM, Ray W. FDA guidance on off-label promotion and the state of the literature from sponsors. *JAMA*. 2008;299(16):1949-51.
15. Turner EH, Matthews A, Linardatos E, Tell R, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252-60. Available at: <http://content.nejm.org/cgi/reprint/358/3/252.pdf>. Accessed February 7, 2009.
16. Gøtzsche PC, Hrobjartsson A, Johansen H, Haahr M, Altman D, Chan A. Ghost authorship in industry-initiated randomised trials. *PLoS Med*. 2007;4(1):e19. Available at: <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1769411&blobtype=pdf>. Accessed February 7, 2009.
17. CMS Medicare Learning Network. Compendia as authoritative sources for use in the determination of a “medically accepted indication” of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen. MM 6191, CR6191. October 24, 2008. Available at: <http://www.cms.hhs.gov/MLNMMattersArticles/downloads/MM6191.pdf>. Accessed February 10, 2009.
18. Agency for Healthcare Research and Quality. Technology assessment. Compendia for coverage of off-label uses of drugs and biologics in an anti-cancer chemotherapeutic regimen. Final report. May 2, 2007. Available at: <http://www.cms.hhs.gov/determinationprocess/downloads/id46TA.pdf>. Accessed February 7, 2009.
19. Abelson R, Pollack A. Medicare widens drugs it accepts for cancer. *NY Times*. January 26, 2009. Available at: http://www.nytimes.com/2009/01/27/health/27cancer.html?_r=2&ref=health. Accessed February 3, 2009.
20. Nimeiri HS, Oza AM, Morgan RJ, et al. Efficacy and safety of bevacizumab plus erlotinib for patients with recurrent ovarian, primary peritoneal, and fallopian tube cancer: a trial of the Chicago, PMH, and California Phase II Consortia. *Gynecol Oncol*. 2008;119(1):49-55.
21. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007;25(33):5180-86.
22. Mayer MJ. Targeted therapy for advanced colorectal cancer – more is not always better. *N Engl J Med*. 2009;360(6):623-25.
23. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med*. 2009;360:563-72.
24. Bach PB. Limits on Medicare’s ability to control rising spending on cancer drugs. *N Engl J Med*. 2009;360(6):626-33.
25. Phurrough S, Jacques L, Ciccanti M, Turner T, Koller E, Feinglass S. Proposed coverage decision memorandum for the use of erythropoiesis stimulating agents in cancer and related neoplastic conditions. May 14, 2007. Available at: <http://www.cms.hhs.gov/determinationprocess/downloads/id203d.pdf>. Accessed February 9, 2009.
26. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Historical information on erythropoiesis stimulating agents (ESA). Available at: <http://www.fda.gov/cder/drug/infopage/RHE/historical.htm>. Accessed February 9, 2009.
27. U.S. Food and Drug Administration. MedWatch. 2008 safety alerts for human medical products. Erythropoiesis stimulating agents (ESAs) - epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp), Update December 2, 2008. Available at: <http://www.fda.gov/medwatch/safety/2008/safety08.htm#ESA2>. Accessed February 10, 2009.
28. Stafford RS. Regulating off-label drug use – rethinking the role of the FDA. *N Engl J Med*. 2008;358(14):1427-29. Available at: <http://content.nejm.org/cgi/reprint/358/14/1427.pdf>. Accessed February 3, 2009.
29. St. Onge EL, Miller SA. Pain associated with diabetic peripheral neuropathy – a review of available treatments. *P&T*. 2008;33(3):166-75.
30. Agency for Healthcare Research and Quality. National Guideline Clearinghouse. Assessment and management of chronic pain. Update July 2008. Available at: http://www.guideline.gov/summary/summary.aspx?ss=14&doc_id=12998&string=Painful+AND+diabetic+AND+neuropathy. Accessed February 10, 2008.
31. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus – a randomized controlled trial. *JAMA*. 1998;280(21):1831-36. Available at: <http://jama.ama-assn.org/cgi/reprint/280/21/1831>. Accessed February 10, 2009.
32. Canadian Agency for Drugs and Technologies in Health. Technology Overview, HTA Issue 49. January 2009. Available at: http://cadth.ca/media/pdf/O0458_Management_of_Neuropathic_Pain_to_e.pdf. Accessed February 13, 2009.
33. Agency for Healthcare Research and Quality. Effective Health Care. Efficacy and comparative effectiveness of off-label use of atypical antipsychotics. No. 6. January 2007. Available at: http://effectivehealthcare.ahrq.gov/repFiles/Atypical_Executive_Summary.pdf. Accessed February 7, 2009.
34. Hall RF, Sobotka ES. Inconsistent government policies: why FDA off-label regulation cannot survive First Amendment review under Greater New Orleans. *Food Drug Law J*. 2007;61:1-48.
35. Kesselheim AS, Avorn J. Pharmaceutical promotion to physicians and first amendment rights. *N Engl J Med*. 2008;358(16):1727-32.
36. Steinman MA, Harper GM, Chren M, Landefeld CS, Bero LA. Characteristics and impact of drug detailing for gabapentin. *PLoS Med*. 2007;4(4):e134. Available at: http://medicine.plosjournals.org/archive/1549-1676/4/4/pdf/10.1371_journal.pmed.0040134-S.pdf. Accessed February 7, 2009.
37. Zimmerman R. A unit of Pfizer is target of lawsuit over its marketing. *Wall Street J*. March 15, 2002:B3.
38. Petersen M. Court papers suggest scale of drug’s use. *NY Times*. May 30, 2003.
39. Armstrong, D. Maker of epilepsy drug used misleading data, plaintiff says. *Wall Street J*. May 30, 2003:B4.
40. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166:1021-26. Available at: <http://archinte.ama-assn.org/cgi/reprint/166/9/1021>. Accessed February 17, 2009.
41. Kmietowicz Z., Eli Lilly pays record \$1.4bn for promoting off-label use of olanzapine. *BMJ*. 2009;338:b217; online first January 23, 2009.