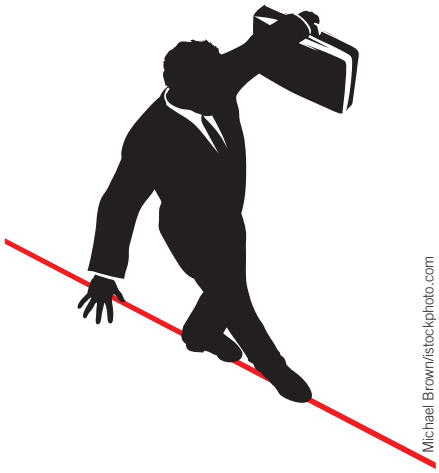
Off-label or off-limits?

Mark Ratner & Trisha Gura

Off-label prescribing is a fundamental fact of life of healthcare systems, but the promotion of off-label uses by drug sponsors is a fundamental sin. Regulators, legislators and drug makers are wrestling to find the right balance.

It has long been held that physicians, not regulators, decide when to prescribe drugs, and for what medical uses. In fact, in the United States, the Food and Drug Administration (FDA) has no authority to regulate so-called 'off-label' use—that is, the perfectly allowable practice of prescribing drugs to treat conditions other than those formally approved by FDA and set out on the label. That said, off-label use may nonetheless be the most misunderstood phenomenon in healthcare. In the United States, it raises complex issues ranging from fundamental social philosophy to First Amendment rights to allocation of government resources to the ultimate unpredictability of clinical science. It is also among the most politically manipulated topics in the current drug safety discussion, especially when blended with its evil twin, the promotion of off-label use by companies, which, with only a handful of exceptions, is a wholly improper activity that constitutes fraud. And the problem is international; in Europe, comparable proportions of off-label use are reported as in North America (**Box 1**). With a controversial new draft FDA guidance proposing to allow the circulation of peer-reviewed literature on off-label uses as educational material receiving a mixed reception, it remains unclear how the system of drug oversight can best expedite the process of bringing valuable new uses of existing drugs to the patients that need them.



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A new proposal would allow companies greater leeway in their use of peer-reviewed literature containing studies of off-label uses for drugs. It is one way the US Food & Drug Administration is attempting to strike a balance between information dissemination and the potential for abusive marketing practices.

Mixed messages

To some, using a drug off-label is a matter of personal choice and in keeping with the right to assume whatever the risk without government interference—like choosing whether or not to wear a seat belt. In that sense, it's a fundamental freedom and a posture unlikely to be swayed by analysis. But it also has its subtleties: in some ways, the debate over off-label use evokes the more complicated one over where the FDA should draw the line between safety and access in deciding whether to initially approve a drug—an analysis that requires a case-by-case review of the degree of risk and reward depending on the nature of the drug, the disease being treated and the patient population receiving it.

Another nuance is that unlike in the seat-belt analogy, where the activity presumably only affects the individual wearer, off-label drug use raises a significant additional issue of potentially denying or delaying a collective benefit—the opportunity to make scientific progress in the best way possible. That's because if a drug can be used off-label, there's less incentive for patients to enroll in randomized, controlled clinical trials because there's the chance they will get a placebo or a drug potentially less effective than the experimental one. This reduces the opportunity to develop the rigorous data needed to assess the drug's safety and usefulness in those as-yet-unapproved settings. Some argue that companies similarly lose the incentive to pursue new and expanded indications for their compounds because they are already commercially available.

"It's a matter of individual autonomy versus societal benefit," explains Christopher Thomas Scott of the Stanford University Center for Biomedical Ethics in California. A similar phenomenon exists for offshore interventions (medical tourism), he notes: a person may well choose to opt out of a randomized clinical trial in favor of a riskier treatment or one not bound by a protocol because they are sick, perhaps dying and want help now; because they don't buy into the societal benefit approach; or because they are suspicious of the bureaucracy associated with FDA-approved trials.

Indeed, the suspicions Scott alludes to—not just of a clinical trials bureaucracy, but of the overall ineffectiveness of regulators and of companies that have built-in incentives to breach appropriate standards of conduct in their pursuit of profits—infuse much of the common perceptions of the off-label phenomenon.

"There's a notion that there's something criminal about it," notes Michael McCaughan, senior editor of Elsevier publications' *The RPM Report* (Washington, DC, USA). People recognize there's a huge compliance issue going on, he says—the potential for companies to cross the line. "You get a strong sense there's something wrong with off-label prescribing, even though it's perfectly legal….The belief is that any off-label prescription must be somehow suspicious and that there must be an evil pharma

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Box 1 European call for harmonization

The situation in Europe bears some similarity to that in the United States: off-label prescribing by physicians is allowed, but promotion by drug companies is not. However, where the two differ is in the muscle behind the regulation. Unlike the United States, which has heavily enforced fraud and antikickback statutes, in Europe, individual member states each have their own regulations for off-label use, which are unclear and lead to improper denials, according to P.G. Casali, in writing on behalf of the European Society of Medical Oncology[3]. In the United States the improper use of the antidepressant drug Paxil (paroxetine, known as Seroxat in the UK), stemming from the withholding of information of the results of clinical trials, led to several lawsuits with judgments and fines imposed against the drug maker, GlaxoSmithKline (Brentford, UK). In the UK, regulators changed the label. According to a report by the BBC[4], Kent Woods, chief executive for the UK's Medicine and Healthcare Products Regulatory Agency (London) bemoaned the lack of effective legislation for prosecuting companies involved with fraudulent claims. Their four-year-long investigation has "revealed important weaknesses in the drug safety legislation in force at the time," he said. Some are calling for harmonization of the regulations through the creation of lists of acceptable indications by the EMEA, which would provide some guidance for off-label use. Such harmonization has been in place for the market approval for drugs for certain indications since 2005. Studies show that some drug categories, particularly in oncology and for pediatric use, are heavily prescribed off-label; as much as 100% in pediatric cancer patients received at least one drug off-label[5]. The fear seems to be that off-label overprescribing has the effect of emasculating the drug regulatory agencies. "The general off-label use of drugs is the death of the idea of regulation," wrote J. Boos, of University Children's Hospital (Munster, Germany) in an editorial in the *Annals of Oncology*[6].

Laura DeFrancesco

company behind it." On the other hand, whenever a patient or consumer who tries to use a drug off-label has trouble getting it, there's an equally strong reaction that it's the greedy insurance company trying to prevent good healthcare.

"They are both going on at the same time, and it's incredible to watch," says McCaughan. "You have [US Representative] Henry Waxman [D-Calif.] simultaneously hauling in prosecutors and yelling at them for not punishing drug companies enough for off-label promotion and other activities, and at the same time he and a lot of people like him are worked up about insurance companies not covering off-label uses, even when, for example, in the Medicare program, the law stipulates what can and can't be covered. There's this real contradiction there." There's a similar push-pull irony over information versus conflict of interest, he points out: after oncologists asked the Centers for Medicare & Medicaid Services (CMS) to expand the list of medical journals whose articles could serve as the basis for reimbursement of off-label cancer drug use—and CMS obliged by expanding the list—it promptly received a letter from Senator Charles Grassley (R-Iowa) probing the conflict-of-interest policies of those journals.

A history and awareness of abuses

Given that regulators have no overt authority over off-label drug use, to McCaughan, the core question is the extent to which people are willing to trust doctors, pharmaceutical companies and other private sector entities to make choices where there is clearly a commercial influence. A series of recent settlements of high-profile investigations of pharmaceutical companies over illicit marketing practices, including the promotion of off-label drug use, makes it easy to stir the pot of distrust (**Table 1**).

According to Taxpayers Against Fraud (TAF; Washington, DC, USA), there are currently more than 180 pharmaceutical fraud cases covering more than 500 drugs under investigation in the United States. Settlement of 16 such cases has resulted in the collection of over $4 billion by the federal and state governments. And although not all involve off-label promotion, every one of TAF's 'top 20' settlements and recoveries under the False Claims Act (a federal law encompassing false claims for payment of government funds, which includes Medicare and Medicaid) involve some flavor of fraud in the healthcare sector.

The most notorious and oft-cited example of off-label abuse is Warner Lambert's scheme to promote its anti-seizure drug Neurontin (gabapentin) for a variety of other neurological uses. According to court papers filed by Pfizer (New York), which acquired Warner-Lambert, more than three-quarters of the Neurontin prescriptions written in 2000 were for unapproved uses (other sources say it is was high as 83%). The New York drug maker ultimately settled the case, which included criminal penalties, for $430 million.

Among biotech firms, Serono Labs, now part of Merck Serono (Geneva), tops the TAF list of offenders with the fourth largest recovery of any kind ever: in 2005, it agreed to pay $704 million to settle charges involving the prescribing and marketing of its Serostim human growth hormone (somatropin), used to fight AIDS-related wasting. Schering-Plough (Kenilworth, NJ, USA) sits in sixth place on the all-time list, having paid $435 million in 2006 to resolve criminal and civil liabilities in connection with illegal sales and marketing programs for four drugs, including its alpha interferon drug, Intron-A.

Amgen (Thousand Oaks, CA, USA) is currently the focus of an inquiry into fraud related to off-label promotion. A former Amgen sales rep in New Jersey has sued the biotech for $10 million, claiming she was fired in retaliation for not complying with what she perceived as an improper marketing campaign for the company's Enbrel (etanercept) tumor necrosis factor alpha inhibitor. In January, the New Jersey attorney general's office subpoenaed Amgen about the matter, and, according to the blog *Pharmalot*, another former Amgen sales rep has come forward describing company directives to sales reps, including pulling patient files from doctors' offices, letter-writing campaigns to patients and insurers, and orchestrating and attending patient outreach seminars—activities that involved off-label promotion, according to the attorney reported to be representing both sales reps[1].

Potentially abusive practices of off-label promotion may be brought to light by whistleblowers, competitors, even physicians. It may not be difficult to determine when marketing practices cross the line into fraud. Still, a major conundrum is whether off-label prescribing is good or bad for patients, and unfortunately, there's little information in this regard. For example, before companies were concerned about prosecutions, they would say to investors, "We think about 40% of the use is off-label." But now, the mere fact of forecasting potential off-label use may suggest evidence of intent to promote such use, making even keeping track of it a risky proposition.

Neither is historical information helpful; it is anecdotal, and largely out of date. According to a survey of office-based physicians reported in the *Archives of Internal Medicine* in 2006, 46% of the prescriptions written for cardiac and anticonvulsant drugs in the year 2001 were off-label. The

Table 1 Selected healthcare-related fraud cases involving off-label use

Company	Product	Amount/year	Activities
Pfizer/Warner-Lambert	Neurontin	$430 million/2004	Before its acquisition by Pfizer, Warner Lambert was investigated by the Massachusetts Attorney General's Office and the Department of Justice (DoJ) for the promotion of its anti-seizure drug for a variety of other neurological uses. Settlement included criminal penalties.
Serono	Serostim	$704 million/2005	Settled charges involving off-label promotion of and kickbacks offered for the prescribing of its human growth hormone, approved to fight AIDS-related wasting, notably through the marketing of an unapproved device used to calculate body cell mass in order to boost drug sales.
Eli Lilly (Indianapolis)	Evista	$36 million/2005	Settlement of claims stemming from a DoJ investigation that found the company had marketed the osteoporosis drug for the prevention of and reduction of risk of breast cancer and for the reduction of risk of heat disease.
Schering-Plough (Kenilworth, NJ, USA)	Intron A; Temodar	$435 million/2006	Payment to resolve criminal and civil liabilities in connection with illegal sales and marketing programs for four drugs, including Medicare claims pertaining to its Intron-A alpha interferon and Temodar brain tumor drug.
Intermune (Brisbane, CA, USA)	Actimmune	$36.8 million/2006	Settlement of charges involving marketing of the drug for idiopathic pulmonary fibrosis, an unapproved use.
Cell Therapeutics (Seattle and Bresso, Italy)	Trisenox	$10.6 million/2007	Settled claims involving off-label marketing of the drug, approved for treatment of acute promyelocytic leukemia, for other cancers and preleukemic conditions, and kickbacks offered for prescribing it.
Medicis Pharmaceutical (Scottsdale, AZ, USA)	Loprox	$9.8 million/2007	Settled charges relating to the promotion of the topical skin preparation to children under ten.
Jazz Pharmaceuticals (Palo Alto, CA, USA)	Xyrem	$20 million/2007	Settled charges relating to the off-label promotion by subsidiary Orphan Medical of the narcolepsy drug for other disorders for which it was not approved, including insomnia and psychiatric disorders.
Bristol-Myers Squibb (New York)	Abilify	$515 million/2007	Settlement of claims including charges that the company promoted the drug, an atypical antipsychotic, for pediatric use and to treat dementia-related psychosis, both of which are off-label uses.
Cephalon	Actiq/Fentora	$425 million/2007	Settled DoJ charges relating to the off-label marketing of its pain narcotic to treat back pain and migraines.

Source: Taxpayers Against Fraud website (http://www.taf.org/); Department of Justice press releases; news reports

next highest market categories were antiasthmatics (42%); allergy medications (34%); psychiatric drugs (31%); and peptic ulcer/dyspepsia drugs (30%). A rough overall number for off-label use is around 20% of all prescriptions[2] (**Fig. 1**).

The number is much higher for cancer drugs, but here again, it's hard to say by how much. The American Society for Clinical Oncology (Alexandria, VA, USA) and the National Comprehensive Cancer Network (Fort Washington, PA, USA) say that more than 50% of cancer therapy is off-label; others in the community put it as high as 70%. But the only traceable source is outdated at best—a 1991 survey by the US Government Accountability Office (Washington, DC, USA) found that more than half of cancer patients (56%) were prescribed at least one drug off-label as part of their treatment regimens.

Whatever the actual number, it's clear that the ability to use cancer drugs off-label is core to therapy—and by all accounts, beneficial to patients.

"If we took away any part of our drug use in oncology we wouldn't be treating cancer," says Charles Bennett, an oncologist at the Northwestern University Feinberg School of Medicine in Chicago and the leader of the Research on Adverse Drug Events and Reports (RADAR) project. "Clearly off-label use is important….It probably is more important in cancer than in other diseases." Beyond the impact on patient care, off-label use is also critical to funneling new drugs into the pipeline: once a cancer drug is approved by FDA, for example, the mechanistic advantage it offers is often found to have applications in more than one type of cancer. What's more, it simply costs too much to obtain full FDA approval in multiple cancers. "Each would cost $700 million and would take 3–5 years," Bennett points out.

It is precisely this niche nature of cancer drug development that has attracted many biotechs, which favor small, targeted clinical programs that can later be partnered with pharmaceutical companies as proof of concept for broader uses that may emerge later.

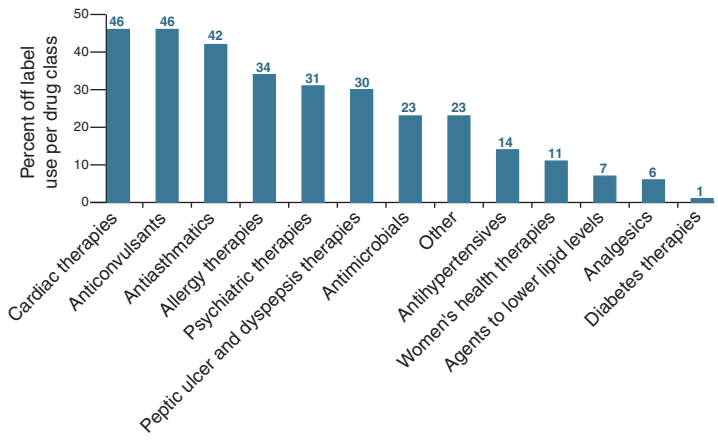

Figure 1 Off-label prescription of drugs by functional class. Reprinted with permission from *Archives of Internal Medicine*, **166**, 1021–1026 (2006).

And off-label use is a perfectly acceptable way to help amass the knowledge.

The perception, however, may be otherwise. "You have two conversations with yourself," explains Peter Pitts, a former FDA associate commissioner and president of the Center for Medicines in the Public Interest (CMPI; New York). "Are companies gaming the system strictly for monetary gain? I think that is certainly part of it," he says. "But I would also like to think that companies who strategically choose a narrow indication to get approval are doing so because they believe their drug can help many people in many different ways beyond the indication they received from the FDA. There is obviously a narrow [business] incentive to do it, but I also believe there is this very strong health imperative as well."

Admittedly, the tactic is not limited to biotech companies. "You develop every drug knowing that medicine will advance and physicians may then use it for many other things," suggests Sara Radcliffe, vice president of Science & Regulatory Affairs for the Biotechnology Industry Organization (BIO; Washington, DC, USA). "I don't know that's particular to biotech companies…that's just the way it is." Nonetheless, off-label use has a special historical resonance with biotechs.

For example, some of the protein therapeutics developed in the 1980s—the interferons, for example—were created because "people could make them with this new recombinant technology. But they didn't know exactly what they would be good for," explains biologics expert Janice Reichert of the Tufts Center for Drug Development (Boston). That's not true for anti-cancer monoclonal antibodies (mAbs), which are targeted, but, for example, Genentech (So. San Francisco) the developer of the mAb drugs Herceptin (trastuzumab, for breast cancer) and Avastin (bevacizumab, for colorectal, non-small-cell lung cancer, and more recently, for breast cancer), is continuing to identify and seek approval for expanded uses for those compounds, either to treat additional tumor types or stages of disease. Rituxan (rituximab), originally developed for treating non-Hodgkin's lymphoma, and non-cancer mAbs, such as Remicade (infliximab), are finding new and expanded immunological indications (**Table 2**).

"It's all part of the life cycle management of drugs, starting with clinical studies, new drug application (NDA) submission to FDA and approval," says Tufts' Joshua Cohen, who

Table 2 Biologics and their expanded indications

Drug	Description	FDA approved new indication (date)	Expanded indication (date)
Rituxan (rituximab)	Chimeric, IgG1κ, anti-CD20	Treating relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma (11/26/1997). In combination with methotrexate to reduce the signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to tumor necrosis factor (TNF) antagonist therapies (2/28/2006).	First-line treatment of follicular, CD20-positive, B-cell non-Hodgkin's lymphoma in combination with CVP chemotherapy (9/29/2006) Slow the progression of structural damage in rheumatoid arthritis (1/25/2008)
Remicade (infliximab)	Chimeric, IgG1κ, anti-TNFα	Reducing signs and symptoms in patients with moderately to severely active Crohn's disease who have an inadequate response to conventional therapies; patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula (8/24/1998). Reducing signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate (11/10/99). Treating active ankylosing spondylitis (12/17/2004). Treating patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (9/15/2005). Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (5/19/2006).	Inhibiting progression of structural damage in patients with rheumatoid arthritis who have had an inadequate response to methotrexate (12/29/2000) Improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate (2/27/2002). Maintenance dosing regimen for nonfistulizing Crohn's disease; reducing signs and symptoms, and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (6/28/2002). Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease (4/1/2003). Treating patients with earlier stage rheumatoid arthritis with moderate to severe disease activity, not previously treated with methotrexate (9/28/2004). Treating psoriatic arthritis (5/13/2005). Inhibiting progression of structural damage of active arthritis (8/11/2006) Improving physical function in patients with psoriatic arthritis (8/11/2006). Treating patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (10/13/2006).
Herceptin (trastuzumab)	Humanized, IgG1κ, anti-HER2	Treating metastatic breast cancer patients whose tumors overexpress HER2 protein and who have received chemotherapy regimens. In combination with paclitaxel for treating metastatic breast cancer patients whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease (9/25/1998).	As part of a treatment regimen containing doxorubicin, cyclophosphamide and paclitaxel for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer (11/16/2006). As a single agent for the adjuvant treatment of HER2 overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline-based therapy (1/18/2008).
Campath-1H (alemtuzumab)	Humanized, IgG1κ, anti-CD52	Treating patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy (5/7/2001)	As a single agent for treating B-cell chronic lymphocytic leukemia (B-CLL) (9/19/2007).

(continued)

Table 2 Biologics and their expanded indications (continued)

Drug	Description	FDA approved new indication (date)	Expanded indication (date)
Humira (adalimumab)	Human, IgG1κ, anti-TNFα	Reducing signs and symptoms and inhibiting the progression of the structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS) (12/31/2002). Reducing signs and symptoms in patients with active ankylosing spondylitis (7/31/2006). Inhibiting the progression of structural damage in patients with psoriatic arthritis (1/19/2006). Improving physical function in patients with psoriatic arthritis (11/9/2006). Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severe Crohn's disease who have had an inadequate response to conventional therapy; and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab (2/27/2007). Treating adult patients with moderate to severe chronic plaque psoriasis (1/18/2008).	Improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs (7/30/2004). Treating recently diagnosed patients with moderately to severely active rheumatoid arthritis who have not received methotrexate (10/3/2005). Treating psoriatic arthritis (10/30/2005). Treating juvenile idiopathic arthritis (2/21/2008).
Erbitux (cetuximab)	Chimeric, IgG1κ, anti-EGF receptor	In combination with irinotecan, treating EGFR-expressing, metastatic colorectal carcinoma in patients refractory to irinotecan-based chemotherapy; as a single agent, treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy (2/12/2004). In combination with radiation therapy, treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (3/1/2006). As a single agent for the treating patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed (3/1/2006).	As a single agent in patients with EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens (10/2/2007).
Avastin (bevacizumab)	Humanized, IgG1κ, anti-VEGF	First-line treatment of patients with metastatic carcinoma of the colon and rectum in combination with intravenous 5-fluorouracil-based chemotherapy (2/26/2004). First-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel (10/11/2006). In combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer (2/22/2008).	As an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer (6/20/2006).

Source: Tufts Center for the Study of Drug Development, Boston

is investigating reimbursement schemes for off-label uses along with Reichert and other colleagues. "There's also a continuation of that phase with supplemental approvals [sNDAs]," he notes, which add new or expanded indications to the drug label. Many sNDAs at one time were significant off-label uses, such as with Avastin.

An active debate over uses

Drug developers, however, don't always apply for an sNDA. And unfortunately, the very existence of off-label use can deter the drug development process in several ways—especially if a new FDA draft guidance expanding the use by companies of peer-reviewed literature about off-label uses is enabled.

For one thing, "FDA's willingness to allow companies to promote drugs for off-label uses could really pull the rug out from under the incentive for sponsors and clinicians and patients to engage in the kind of randomized trials that are absolutely essential to defining appropriate drug use," explains Jerry Avorn of Harvard Medical School and Brigham and Women's Hospital (Boston).

If companies can more easily promote a drug, they will be more inclined to spend their dollars on marketing and promotion instead of actually doing the research, he suggests. "In the current situation, where it is rather difficult for a company to promote a drug's use off-label for a cancer other than the one for which it is approved, [the company] needs to be able to produce evidence that [the drug] works for that [cancer]. If we skip that requirement, then there is no reason to expect that the company will have any incentive to make the substantial investment that it has to for doing those studies. And it will be also much tougher for doctors to find patients who will enroll in clinical trials."

At the same time, Avorn is quick to point out that off-label use is sometimes quite appropriate—a fact acknowledged by both FDA and by clinicians and others who study drugs, he adds. Avastin now is being used off-label to treat age-related macular degeneration. But in an ironic twist to the usual scenario where off-label use benefits the drug maker, its use off-label has cut into sales of another Genentech drug, Lucentis (ranibizumab), a Fab fragment of the Avastin antibody that is much more expensive. The National Eye Institute (Bethesda, MD, USA) recently launched a trial comparing the efficacy of the two (**Box 2**).

There will sometimes be a very reasonable evidence-based clinical trial–driven use of a drug for an indication that has not yet made it into the FDA label, as is the case in oncol-

Box 2 Avastin: compounding the off-label issue

In February, the National Eye Institute (NEI) of the National Institutes of Health launched a head-to-head trial comparing the Genentech drugs Lucentis (ranibizumab) and Avastin (bevacizumab) to treat age-related macular degeneration (AMD). Both molecules are derived from the same mAb. In a press release announcing the multicenter study, the NEI noted that Avastin, approved for treating colorectal cancer, "has been widely used to treat advanced AMD."

Lucentis, an antibody fragment, is a much more expensive drug: $2,000 per injection versus $40–50 for a reformulated dose of Avastin. Genentech has barred sales of Avastin to pharmacies that were repackaging it for use in treating AMD—a decision that drew the ire of ophthalmologists at the annual meeting of the American Academy of Ophthalmology last fall.

In defending its decision to limit the availability of Avastin, Genentech cited FDA concerns related to the sterility and repackaging of the drug for ocular use at the pharmacy level and also with respect to manufacturing standards, leading, it said, to the destruction of four batches of Avastin deemed unsuitable for use in the eye after a routine inspection—a loss of more than 350,000 vials with a market value of more than $200 million.

The company said the FDA actions and the potential for future actions "necessitated a change in our policy toward compounding pharmacies." But according to a June 18, 2008, posted in *The Wall Street Journal Health Blog*, FDA inspectors told Senator Herb Kohl (D-Wisc.) that the issue was broader; namely, "the lack of effective processes to know what was in those four lots," leading to their being considered unfit for use in any indication[7].

Kohl has been investigating whether Medicare should pay for Lucentis. The NEI trial could answer that question: its estimated primary completion date (when final data are in to measure primary outcomes) is February 2010.

ogy with combination chemotherapy. The question for Avorn is not does this or doesn't this happen, or is it a good thing or a bad thing, but rather: How can the drug evaluation and approval process be made efficient and responsive enough to be able to know that when there is an important use of the drug, it actually has been studied and gets added to the label relatively quickly? "I would have companies present their data to the FDA in a more rapid manner so that if something does work, it gets into the label," he says.

On the other hand, Scott Gottlieb, a former FDA official and currently a resident fellow at the American Enterprise Institute (AEI; Washington, DC, USA), has pointed out that even when companies do this, historically it's been harder to get an sNDA approved than it should be. In some ways, it's more difficult than the original application—because the FDA had reputedly used those supplements as a way to get more information out of the sponsor than is necessary to support an expanded indication. For example, in his view, the adjuvant use of Herceptin in breast cancer was initially slower than it should have been because the approval was too slow.

Herceptin was widely used in advanced breast cancers for years and was recently found to cut recurrence by about half in some patients with earlier-stage tumors. But in a December 2007 editorial in *The Wall Street Journal*, Gottlieb wrote that although those results were first published early in 2005, and that new use was approved by the FDA in late 2006, doctors didn't embrace it right away. "You can bet that folks at Genentech, living under the thumb of the Philadelphia US attorney, weren't about to talk up the landmark findings," he commented in the article, referring to an ongoing federal fraud investigation into whether Genentech had inappropriately shared information with physicians about unapproved uses for another of its drugs, Rituxan. "The use of Herceptin in early-stage breast cancers was roughly half what you'd expect for the almost two years between publication of the study's findings and the FDA nod," Gottlieb wrote. "It's hard to deny that some of those Herceptin-eligible women who didn't get the drug are now unnecessarily doomed." At a May 2008 AEI briefing in Washington, DC, on off-label use, Gottlieb displayed a Genentech slide showing market uptake for Herceptin that suggests 20% of the physicians were early adopters off-label, whereas 20% still don't use the drug this way, even though the evidence is now overwhelming.

Irrespective of whether Genentech was actually cowed by the Rituxan investigation, Gottlieb is probably correct that the world of compliance has a new-found effect on corporate decision making.

According to Northwestern's Charles Bennett, almost every adjudication of healthcare fraud has been accompanied by a corporate integrity agreement (CIA), which often includes mandatory ethics training, hotlines for employees to report fraud and abuse, and other tools corporate compliance offices have never had before. Effectively, "we have restructured the system," he points out. And a by-product has been the creation of corporate compliance departments within companies that potentially do more harm than good, by adopting ultraconservative and literalist policies about what marketers can and cannot do.

"If you tell anybody about off-label uses, if you are a pharmaceutical company, you are at least at risk of prosecution or very large civil fines," explains Alan Bennett (no relation) of the law firm Ropes and Gray (Washington, DC, USA). Even asking a question internally about what's permissible discussion and what is not can delay an absolutely appropriate rollout or scientific program. "You end up having a corporate compliance culture that looks at the worst-case scenario," suggests *The RPM Report*'s Mike McCaughan. That becomes counterproductive because the result is that if a marketer can possibly proceed without asking for compliance help, he or she will. "Where people could benefit from good compliance input, the last thing they want to do is ask for it," says McCaughan. "There are clearly more bad actors than the industry apologists would have you believe, but there are also more well-intentioned people who aren't setting out to break the law, who get caught up in nightmare scenarios because they didn't get the right advice at the right time."

Off-label but on compendium

Companies must also be mindful of the role of payers when they contemplate the realities of off-label use. Indeed, in the United States, CMS is likely to hold the greatest sway over a drug's fate in the marketplace—especially for biologics, which for the most part are expensive drugs that usually target life-threatening conditions, and are reimbursed under Medicare Part B.

"Payers don't make a binary decision, it's usually a 'yes but'," explains Tufts' Cohen. "They will pay for virtually any biologic that comes down the pike and goes into Part B. However, it gets complicated because the restrictions on whether a use is on- or off-

label become the way in which CMS can curtail or contain cost growth." Patients and physicians have one perspective and the payers another, he says: "Physicians think of the world in terms of unlimited resources but the payers think of a limited one."

At least 50% of biologics in the US market are paid for by CMS, either through Medicare or Medicaid. And understandably, CMS places more restrictions on off-label use of biologics than on on-label sNDAs, Cohen explains. "CMS will cover off-label use based on peer-reviewed data, especially if the drug has received a positive recommendation in a compendium listing, such as the USP DI [United States Pharmacopeia Dispensing Information] or the NCCN [National Comprehensive Cancer Network]," he says. "But if a drug is in a compendium and it has a positive recommendation and it is in another one and it has a negative recommendation, that negative recommendation can overrule the positive one for off-label uses." Furthermore, for outpatient drugs under Part D of the Medicare program, restrictions exist on whether or not peer-reviewed literature counts as a condition for coverage. So if a drug is reported in the literature as a reasonable use of resources because it does what it is supposed to do off-label, literature gives CMS a reason to reimburse for Part B drugs, the section that addresses drugs administered by physicians, but not for Part D (self-administered drugs). "All of this is a ratcheting up," he concluded. "They are making the restrictions on off-label uses more stringent."

That gives companies incentive to get an sNDA, particularly for drugs traditionally falling under Part B. "You're going to get an increasing number of drugs that will be used off-label that will not be approved for reimbursement based on peer-reviewed literature," Cohen suggests. "That's an important fact." Moreover, he says, although the Tufts survey is in the early stages of data gathering, the researchers are finding that physicians are saying that Medicare rules are essentially applied across the board. "We're noting that payers are saying this too," states Cohen. "Not all, but they are saying we really don't have the time in-house to create consistent policy guidelines—we look to CMS for guidance, particularly for the biologics paid for by CMS."

New guidance

Even as CMS is changing the landscape, the landscape is also changing for CMS, owing to the new FDA draft guidance on reprint practices. It would allow companies greater leeway in the use of peer-reviewed literature containing studies of off-label uses as educational materials.

One main goal of the guidance is to give clarity to companies around what is permissible and what is not. But some are concerned that, as Jerry Avorn points out, it will loosen some of the restrictions on the dissemination of peer-reviewed literature discussing off-label drug uses, the measure can only encourage more off-label use and potentially discourage the initiation of desirable clinical trials.

"The proposed policy the FDA has floated for consideration is not wise," declares Steve Nissen of The Cleveland Clinic in Ohio. "My view is that drugs should be used for those indications for which they have been studied, where there is good, careful data that has been reviewed by the FDA. We should have public policies that encourage conducting high-quality randomized trials that will stand the scrutiny of the FDA. And the way to do that is to force them to be submitted to get a label claim. Once you lower the standard and say that a drug can be marketed for a use for which it has not been rigorously tested nor reviewed by the agency, then I think you're on a slippery slope."

"I don't think the guidance is anything new," counters Ropes and Gray's Alan Bennett. "I think the guidance simply provides clarity. If you go back and look over the course of the last 15 years, first everyone thought article dissemination was scientific exchange and was legal. Then FDA geared up DDMAC [the FDA Division of Drug Marketing, Advertising, and Communications] and all of a sudden everyone thought it was illegal."

These concerns were put to rest in a series of activities, Bennett points out, starting in 2000, with the US Supreme Court decision in Washington Legal Foundation versus FDA (the WLF case), which found that Congressional and FDA attempts to restrict information were unconstitutional. Then in 2002, the Congress legalized article dissemination under certain restraints, but got rid of the guidance documents—and therefore impact of the WLF case. Now that legislation has expired.

"Companies are really anxious now," adds Sandra Dennis, BIO's deputy general counsel for healthcare regulatory affairs. "The guidance is so important in terms of [defining] what's acceptable and what might be a safe harbor….And there's even less guidance now on what the Department of Justice [DoJ] thinks is appropriate." Because of the financial penalties, she says, "DoJ can get a lot of money for what used to be off-label communications but now has become fraud and abuse. It has morphed into huge investigations…it seems that almost every major company is under investigation."

There's an underlying lack of clarity under current regulations, Alan Bennett says. "Nobody really knows what the rules are: there are promotional disseminations, advertising, brochures and the detail force, all of which might be subject to one set of rules. And then there is [educational] dissemination, which at least some of us would say might be subject to a different kind of regulatory construct, which has a constitutional protection to it." There are also other related issues that cry out for clarification, such as when is it appropriate for a company to talk to a formulary committee before approval, to give them data that might permit reimbursement of a drug when it is approved.

But a journal article that suggests a use does not mean that there is essentially adequate evidence that that usage is both safe and effective. "The medical literature has many good manuscripts, but there are also many manuscripts that ultimately turn out to be wrong or are somehow biased," says Nissen. "It's the job of the FDA to review evidence for benefits and risks, and make a determination whether the benefits exceed the risks. It's not going to be done if this policy is followed."

In Congress, Representative Henry Waxman and others have argued that any loosening of current rules is too much, because journal articles can also be a powerful persuader of physicians. William Hubbard, a former FDA associate commissioner and now an adviser to the Alliance for a Stronger FDA (Washington, DC, USA), explains: "Someone sees a prestigious journal's name and a long list of credible doctor's names, then they say, 'Gee if those guys found this off-label use is a good one, why should I question that?'" Even the label itself has limited power to counter a clever detailer's pitch. "I think the FDA would love for doctors to read the package inserts," he laments. "But they don't."

CMPI's Peter Pitts agrees that for better or worse, doctors don't have the time to sit down and carefully read medical articles discussing off-label use, or even physician package inserts. "They are learning information anecdotally through patients and colleagues at conferences and through conversations with pharma reps," he suggests. "And when it comes to having reps hand a physician a reprint of a medical article that discusses an off-label use, I think it very clearly and unambiguously falls under the safe harbor of the free and fair dissemination of information."

The most important manifestation of the WLF case, Pitts argues, is that even with the FDA under intense political and media and public pressure, "it came forward with a draft regulation that very unambiguously said that this was permissible and allowable and that the FDA has no business standing in the way. Yet you still had people like Mr. Waxman, for reasons that are completely mysterious to me, feeling like the doctors shouldn't be privy to relevant data when it comes to treatment." The issue, however, is only whether companies should be allowed to be the conduit for such information. And there are other means of dissemination, for example, the use of academic detailing, a decades-old idea now taking hold (**Box 3**).

In the end, it will be up to the FDA to monitor whether this journal article policy is working, says Hubbard, perhaps through DDMAC. "If it turns out that off-label use goes up based on these journal articles, it could be a marker for a problem," he says. "On the other hand, if it turns out that doctors are getting this good information and the off-label use ultimately gets approved, and that has been beneficial, we need to know that too."

First steps in a process of renewal?

In one respect, the reprint guidance is a step toward FDA's reestablishing its presence in

Box 3 Counter drug detailing: safeguarding the system?

As a new FDA guidance opens physicians' doors to a flux of peer-reviewed, off-label information, an old medical counterintelligence program is now catching fire. The COINTELPRO stems from a practice known as 'drug-detailing', in which a biotech or pharmaceutical sales representative offers a doctor information about a company's new drugs, with the intent of persuading the physician to prescribe them. Many physicians have long been skeptical about drug detailing—whether for on- or off-label use. After all, a drug-rep's first aim is profit rather than patient well-being. Still, many busy doctors admit that they have come to rely on drug detailing to keep them abreast of the latest prescribing trends.

Enter the new FDA draft guidance, issued in April, in which it is proposed that drug reps could hand physicians reprints of peer-reviewed journal articles that detail a drug's possible uses, off-label. Although the practice is backed by the tenet of free speech and the value of spreading beneficial scientific information, still the idea of using journal articles for off-label promotion has left some physicians squeamish.

"I don't think it is healthy for doctors to learn much of what [they] know from sales reps," says internist, geriatrician and pharmaco-epidemiologist Jerry Avorn, at Harvard Medical School and Brigham and Women's Hospital (Boston).

With this perspective, he in 1983 invented a way to fight back with 'counter-drug detailing'. In essence, the practice co-opts the best methods that drug companies have developed to detail their products; that is, visiting physicians' offices, offering free food, and speaking in discussion groups or at podiums. Avorn's method, however, applies the practices to teaching healthcare practitioners, for example, about evidence-based medicine or offering general balanced knowledge to help make better prescription decisions.

"It is like a spy-versus-spy thing," says oncologist Charles Bennett, at Northwestern University's Feinberg School of Medicine (Chicago).

Indeed, the 'agent' drug reps now parry against the 'operative' academic reps, the latter outfitted with medical education gear, including evidence-based studies, outcomes data and details about prescription habits. Like traditional drug reps, academic drug detailers try to persuade physicians. But not necessarily to prescribe more of a particular drug. In fact, sometimes the best practice is to prescribe less; prescribe generically; or prescribe an older, cheaper drug that works just as well as a high-tech new one, says Avorn.

The whole idea traces back to a paper Avorn published in 1983 in the *New England Journal of Medicine* (*NEJM*). In a controlled, randomized clinical trial, Avorn and his colleagues showed that doctors given balanced information about three drug groups—cerebral and peripheral vasodilators, an oral cephalosporin and propoxyphene—subsequently reduced their inappropriate prescription, as well as halved Medicaid's costs[8]. Nearly a decade later, Avorn's group furthered their cause with another *NEJM* paper. It demonstrated that a physician education program could reduce excessive sedation of nursing home residents—without compromising their overall behavior and cognitive function[9].

Most recently, counter-drug-detailing efforts have spread beyond the realm of experimental study into the real world. The states of Pennsylvania, New York, Vermont, New Hampshire and Maine, as well as the District of Columbia, have all anted up millions for help in establishing their own academic detailing programs. In fact, New York State and the District of Columbia, among others, have actually passed laws mandating such activities.

Meanwhile, at the federal level, US Senate Special Committee on Aging Chairman Herb Kohl (D-Wisc.) on March 12 held a hearing to consider creating a federal academic detailing program.

"Without academic detailing, physicians may not have access to information about the full array of pharmaceutical options, including low-cost generic alternatives," concluded Senator Kohl in a press statement.

For this reason, he, along with Senator Dick Durbin (D-Ill.), are jointly introducing a bill in Congress to fund academic detailing. The legislation would create a grant program to produce appropriate educational materials for doctors and train medical professionals to serve as such academic detailers. The bill is slated for introduction this year.

Back in academia, Avorn has continued his efforts to expand his own detailing efforts. His group has posted a website (http://www.rxfacts.org/) through an entity known as Independent Drug Information Service. The site provides information on clinical topics, government drug benefits and relevant links to give physicians a noncommercial source of the latest drug trends and findings.

At the same time, financing for such detailing programs is abounding—and from disparate sources, everything from licensing fees imposed on drug sales reps, to monies budgeted out by groups, such as Kaiser Permanente, to grants from state governments, whose "Medicaid budgets are getting busted by their drug bills," says Avorn.

In addition to monetary resources, such a program also requires human resources. Avorn says those are coming from a stable of nurses and pharmacists, who are well-versed in the science but, because of other duties in their careers, often didn't have the chance to tap their full knowledge.

"We have had no difficulty finding people who want to do this line of work." Avorn says. They say, "Thank god I can use all this knowledge that I had learned about drugs to teach people about how to do drug therapy."

Ironically, some academic detailers are actually former drug reps, "crossing over from the dark side," Avorn says.

Box 4 The Fentora example

On May 6, the biotech company Cephalon appeared before a joint meeting of two FDA advisory committees seeking to have the labeling for their Fentora (fentanyl) pain killer expanded from covering breakthrough pain in cancer to covering other kinds of breakthrough pain as well.

"The most startling statistic that came out of this meeting is that 80% of the current use of Fentora is off-label," notes Ira Loss of Washington Analysis. "Not only is the label for its use narrow, Fentora is a class II narcotic, so it also has prescribing limitations presumably enforced by the Drug Enforcement Administration." Fentora can be lethal when used by children or the elderly. As part of its petition, and in accordance with FDA's desire to assure that Cephalon had workable plans to prevent, monitor and intervene in cases of misuse or abuse, the company presented a risk management plan for monitoring its proposed expanded uses of the drug.

"You could see the agony in the FDA people's faces because they don't want to be saddled with the blame for denying people who really need the pain killer access to it," Loss says. But they were faced with the obvious fact that the company's past efforts at controlling the drug's distribution had not worked, leading to the obvious question: how about if you apply your program to the existing label and see how it works?

The FDA's new authority under the 2007 FDA Amendments Act (FDAAA) to compel companies to construct post-marketing surveillance plans is not directed at off-label drug use—logically it can't be, as the agency does not have power to regulate off-label use. But the good news is that despite the inability to have controlled or even monitored its off-label use in the past, it may be able to do so now, if indirectly. Under FDAAA, the agency is scheduling periodic reviews of the success of post-marketing surveillance programs for the drugs it approves. As the Fentora case shows, that information will be prominent in evaluating submissions for new and expanded uses of approved drugs, and may even reach back to affect existing post-marketing surveillance and risk management programs.

The committees voted 17–3 against recommending the expanded uses for Fentora. The process is "a great example of the new authority for FDA to force the sponsors to keep track of off-label use and report everything they know to FDA about off-label use," claims Michael McCaughan, senior editor of *The RPM Report*. "If nothing else, we've got that now," he says, adding that "it will keep happening more and more. It will be very product specific and issue specific, so if you're trying to sell an easily abusable drug like fentanyl, you can expect that going forward you will be keeping careful check of who's getting it and you are going to be disclosing that to FDA, probably discussed at an advisory committee, and there will be a lot more data about off-label use product by product."

an area dominated recently by prosecutors instead of regulators. And that's in keeping with the whole notion of increasing the agency's risk management authority as a necessary adjunct to drug approvals—an area where FDA's powers were significantly expanded with the passing of the 2007 FDA Amendments Act (FDAAA) last September.

One of the ways to think about the risk management process is as an opportunity for FDA to start to say it will permit some kinds of off-label uses and will block others. It has already started to do this. For example, in part as a result of the poor performance of an existing risk management program, in May it decided to turn down Cephalon's (West Chester, PA, USA) request to expand the use of the pain drug Fentora (fentanyl) (**Box 4**).

That doesn't necessarily mean curtailing a drug's availability. Last year, working with Biogen Idec (Cambridge, MA, USA), the sponsor of the multiple sclerosis (MS) mAb Tysabri (natalizumab), which had been shown to cause a rare but life-threatening side effect, FDA felt comfortable ensuring that only the first indication MS patients would get Tysabri and only after they are fully informed of the risks of taking it. There similarly may be less reason to hold a product hostage because FDA can now place a class warning on a product under FDAAA. That means they may have less incentive to extort more information from drug sponsors under the sNDA process—if you believe Scott Gottlieb that that is what they do now.

"You can argue that now that the agency has the authority to mandate post-market studies, they will no longer use the sNDA process to try and get data to resolve lingering doubts and will instead mandate that sponsors conduct separate studies," says Gottlieb. "But it is likely going to be the case that the sponsors will still try themselves to wrap the safety studies into whatever ongoing efficacy studies they have, to help save costs and preserve patients. So the sNDA process will still be less efficient than it could be," he contends.

Irrespective of the strategic impact on sNDA filings, it's clear that FDAAA gives the agency new muscle to evaluate the effects of off-label usage. "Like it or not, the premise behind the FDAAA authority, the reason they claimed it in the first place, is that FDA realized that they can put whatever they want in the labeling, but it has an unpredictable impact on how the drug is actually used," McCaughan concludes. "Even when FDA knew for certain, and agreed with the sponsor with the best intentions, that certain types of patients should not get a particular medicine, all too often they got it anyway." And from the FDA's point of view, they were being held responsible for that—certainly by politicians.

As with its other monitoring activities, the post-FDAAA question now becomes whether FDA will have the resources and be able to acquire the skill sets to help it determine the impact of off-label use. And the answer to that could differ tremendously depending on the outcome of the presidential election this fall.

"It's very hard to get the politics out of this," says Ira Loss of Washington Analysis (Washington, DC, USA). "There will be a new FDA commissioner regardless of which party wins [the presidency]. That person deserves a honeymoon, and maybe during that time people can have rational discussions instead of trying to use every little thing that doesn't go quite right as a political club to bang the other side or the FDA over the head."

1. Silverman, E. Amgen and Enbrel marketing: crossing another line? *Pharmalot* (February 6, 2008) <http://www.pharmalot.com/2008/02/amgen-enbrel-marketing-crossing-another-line/>
2. Radley, D.C. *et al. Arch. Intern. Med.* **166**, 1021–1026 (2006).
3. Casali, P.G. *Ann. Oncol.* **18**, 1923–1925 (2007).
4. BBC News. Tighter drug trial laws promised, March 6, 2008.
5. Conroy, S., Newman, C. & Gudka, S. *Ann. Oncol.* **14**, 42–47 (2003).
6. Boos, J. *Ann. Oncol.* **14**, 1–5 (2003).
7. Goldstein, J. The FDA contradicts Genentech on eye drug. *The Wall Street Journal Health Blog* (June 17, 2008) <http://blogs.wsj.com/health/2008/06/17/fda-contradicts-genentech-on-eye-drug/>
8. Avorn, J. & Soumerai, S.B. *N. Engl. J. Med.* **308**, 1457–1463 (1983).
9. Avorn, J. *et al. N. Engl. J. Med.* **327**, 168–173 (1992).