

## Regulatory Actions on the Off-Label Use of Prescription Drugs: Ongoing Controversy and Contradiction in 2009 and 2010

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A letter by Zheng and Xu in this issue of *JMCP* spotlights a consensus statement on off-label medication use, written by 20 senior chief pharmacists from 17 hospitals in the Guangdong province of China in March 2010.<sup>1</sup> The statement's provocative recommendations include the imposition of requirements that (a) the off-label drug should be "irreplaceable for treatment of the patient," that is, no drug labeled for the indication is available; (b) the off-label use must be "submitted and approved by the hospital's pharmacotherapy committee and hospital ethics committee" except in emergency situations; and (c) informed consent for off-label use must be obtained from the patient or a legal representative.

The letter comes on the heels of nearly 2 years of heightened debate in the United States over the use of and payment for drugs prescribed to treat indications for which they are not approved by the U.S. Food and Drug Administration (FDA). Triggered by several factors—including U.S. Department of Justice (DOJ) litigation against pharmaceutical companies for off-label promotion, new guidance for "Good Reprint Practices" promulgated by the FDA in January 2009 to clarify the types of medical literature deemed acceptable for distribution to physicians, and the passage of the Affordable Care Act of 2010—the controversy has drawn the attention of numerous stakeholders with different and sometimes sharply conflicting perspectives. In March 2009, we noted that positions on off-label drug use taken by different federal agencies appeared inconsistent, with the DOJ's legal actions against off-label marketing becoming increasingly intense even as the FDA slightly relaxed its stance against the practice and the Centers for Medicare & Medicaid Services (CMS) expanded Medicare coverage for off-label use of chemotherapeutic drugs.<sup>2</sup> Since that time, the controversy has intensified, with stakeholders adopting positions that seem to allow little or no ground for compromise.

### Justice Department Actions Against Off-Label Marketing Continue

Litigation brought by the DOJ against pharmaceutical manufacturers for allegedly engaging in off-label promotion, about which we wrote previously,<sup>2</sup> continued to capture headlines in 2009 and 2010. On April 27, 2010, AstraZeneca announced that it would pay \$520 million, including \$302 million to the federal government and \$218 million to state Medicaid programs, for off-label marketing of the antipsychotic medication quetiapine (Seroquel) from January 2001 through December

2006.<sup>3</sup> Illegal activities alleged by the DOJ included promotions for "aggression, Alzheimer's disease, anger management, anxiety, attention deficit hyperactivity disorder, bipolar maintenance, dementia, depression, mood disorder, post-traumatic stress disorder, and sleeplessness."<sup>3</sup> Allegations also included the company's recruitment of "doctors to give promotional speaker programs on unapproved uses for [quetiapine]," to "conduct studies on unapproved uses of [quetiapine]," and to "serve as authors of articles that were ghostwritten by medical literature companies and about studies the doctors in question did not conduct."<sup>3</sup> These studies, according to the DOJ complaint, became "the basis for promotional messages about unapproved uses of [quetiapine]."<sup>3</sup> A *New York Times* account of the settlement reported that company emails, disclosed as part of separate civil lawsuits, suggested "buried" evidence of weight gain in quetiapine users and the use of a "great smoke-and-mirrors job" on studies that produced unfavorable findings for the drug.<sup>4</sup> However, the DOJ announcement in April 2010 reported that AstraZeneca had "brought certain conduct to the attention of the government" in March 2006 and "then cooperated in the investigation of the allegations,"<sup>3</sup> and the manufacturer has denied the government's allegations.<sup>5</sup>

A similar announcement was made on September 1, 2010, when Allergan agreed to plead guilty to a criminal misdemeanor charge of "misbranding" botulinum toxin (Botox) from 2000 to 2005 for off-label indications that included headache, pain, spasticity, and juvenile cerebral palsy.<sup>6,7</sup> If the guilty plea and sentence are accepted by the U.S. District Court, the manufacturer's total payout will be \$600 million, including financial penalties of \$375 million to resolve the criminal charges and a settlement of \$225 million payable to states and the federal government to resolve civil charges of off-label marketing for a different time period, "from 2001 through at least 2008."<sup>6</sup> The DOJ alleges that although botulinum toxin was approved for "only four rare conditions," the manufacturer "made it a top corporate priority to maximize sales of far more lucrative off-label uses that were not approved by [the] FDA... [and] demanded tremendous growth in these off-label sales year after year, even when there was little clinical evidence that these uses were effective."<sup>6</sup> Notably, however, the manufacturer's announcement of the settlement points out that use of botulinum toxin for "the treatment of increased muscle stiffness in the elbow, wrist and fingers in adults with upper limb spasticity, the most substantial use during the relevant

time period,” was approved by the FDA in March 2010, and an FDA decision on the application for another indication named in the complaint, chronic migraine headache, is expected sometime in 2010.<sup>7</sup>

Two weeks later, on September 15, 2010, the DOJ announced that Forest Pharmaceuticals had agreed to pay a total of \$313 million in fines and penalties to resolve civil and criminal allegations including off-label promotion of citalopram (Celexa) and escitalopram (Lexapro), as well as distribution of a sodium levothyroxine product (Levothroid) in noncompliance with a 1997-2003 FDA phase-down for numerous orally administered levothyroxine sodium drugs that had been on the market since the 1950s without FDA approval.<sup>8</sup> If the settlement is approved by the U.S. District Court for the District of Massachusetts, the manufacturer’s outlays will include a total of \$164 million in criminal penalties and an additional \$149 million to resolve civil complaints filed under the False Claims Act. The primary complaint of off-label promotion involved marketing citalopram and escitalopram for the treatment of depression in children and adolescents when the drugs were approved only for the treatment of depression in adults; escitalopram was later approved on March 19, 2009, for the treatment of major depressive disorder in adolescents aged 12 to 17 years. As in previous cases, the DOJ complaints about off-label marketing of the 2 antidepressants alleged improper influence over physicians, including promoting “pediatric use of [citalopram] in sales calls to physicians who treated children and adolescents, and hiring outside speakers to talk to pediatric specialists about the benefits of prescribing [citalopram] to children and teens.” The manufacturer was also accused of selective presentation of clinical trial results by publicizing the results of a positive clinical trial of the use of citalopram in adolescents while ignoring the “negative results of a contemporaneous double-blind, placebo-controlled European study” of the same indication.<sup>8</sup>

Like previous announcements of settlements reached with pharmaceutical manufacturers over allegations of off-label promotion, the DOJ communications about the 3 cases sounded the siren of patient safety, mentioned 10 times in the announcement about botulinum toxin using terminology like “threatens public health” and “unsafe and ineffective drugs.”<sup>6</sup> Importantly, another point emphasized in the DOJ announcements was a purported violation of the doctor-patient relationship due to off-label marketing. For example, in describing the actions taken against AstraZeneca, U.S. Attorney Michael L. Levy stated that “when pharmaceutical companies interfere with the FDA’s mission to insure that drugs are safe and effective, they *undermine the doctor-patient relationship and put the health and safety of patients at risk*. . . . People have a legal right to know that . . . their *doctors’ judgment* has not been affected by misinformation from a pharmaceutical company trying to boost revenues.”<sup>3</sup> (emphasis added). U.S. Attorney Laurie Magid underscored the

same points in describing an agreement with Eli Lilly that was announced in January 2009 for alleged off-label marketing of olanzapine (Zyprexa).<sup>9</sup> Arguing that off-label marketing had put “*innocent people in harm’s way*,” Magid added that patients “*have an absolute right to their doctor’s medical expertise*, and to know that their *health care provider’s judgment* has not [been] clouded by misinformation from a company trying to build its bottom line.”<sup>9</sup> (emphasis added).

The 3 DOJ announcements also shared what appears to be an escalating “war of words” against off-label promotion, including references to companies that “take billions of dollars directly out of taxpayers’ pockets” and “violate the [Food, Drug and Cosmetic Act] for their own financial gain.”<sup>3,6,8</sup> The most recent DOJ announcement used especially strident language, referring to “individuals and companies who seek to line their pockets at the expense of the health care system,” failure to “be law-abiding corporate citizens,” and, in describing the effect of the manufacturer’s actions on the Department of Veterans Affairs, “[distribution of] unapproved drugs to . . . our nation’s heroes.”<sup>8</sup>

The 3 cases had something else in common—payments to a total of 10 “whistleblowing” company employees made under the “qui tam” provisions of the False Claims Act, totaling \$96.8 million for the 3 settlements.<sup>3,6,8</sup> Notably, both of the whistleblowers in the AstraZeneca case, who shared a total of \$45 million as part of that settlement, were “repeat whistleblowers” who had “blown a whistle” in previous legal actions.<sup>10</sup> One had received settlements in several disputes including \$14.5 million in a 2009 settlement between the DOJ and Pfizer over alleged improper marketing of ziprasidone (Geodon),<sup>10,11</sup> and the other had received an undisclosed share of the 2009 DOJ settlement with Eli Lilly over olanzapine.<sup>10,12</sup>

### ■ Growing Concerns About Dangers of Off-Label Drug Use

The patient safety theme was resounded in news accounts of the dangers of off-label drug use that were published during the summer of 2010. On August 30, 2010, noting that an estimated 89 million of 423 million prescriptions filled in Canada in 2009 were for off-label uses, Canadian news sources recounted the story of a patient who developed suicidal symptoms and severe depression after being prescribed gabapentin off-label for “nerve pain in her leg.”<sup>13</sup> Citing the concerns of critics that “off-label prescribing can amount to an uncontrolled experiment, and that not only do most patients not know when a drug is being prescribed for a condition for which it has not been approved, neither do most doctors,” the Canadian report highlighted recommendations for tougher restrictions on off-label promotion of drugs. Among the recommendations under consideration in Canada, the story reported, was requiring informed consent from patients for every off-label use, “something physicians are under no obligation to do now.” Notably,

the patient described in the article is suing the manufacturer of brand Neurontin (Warner-Lambert/Pfizer), although she took generic gabapentin. Her attorneys argue that the manufacturer's actions in promoting the brand drug in the 1990s contributed to off-label use even after patent expiration.

The Canadian report was published just 2 days after a *Milwaukee Journal-Sentinel* article described the change in bone morphogenetic protein-2 (BMP-2, INFUSE; Medtronic) "from revolutionary advance to public health alert" because a "series of complications and side effects have piled up since 2002," especially in off-label use conditions, which reportedly constitute up to 85% of uses of the drug.<sup>14</sup> Side effects of concern include ectopic bone formation, painful seroma, life-threatening swelling in the neck and throat following cervical spine fusion, and bone resorption or remodeling.<sup>14-16</sup>

Also in August 2010, the *FDA Patient Safety News* reported that GlaxoSmithKline had in May 2010 issued a warning to health care professionals "about the risk of thrombosis if patients with chronic liver disease are treated with Promacta (eltrombopag)." The warning noted that eltrombopag is currently "approved to treat thrombocytopenia in certain adult patients with chronic idiopathic thrombocytopenic purpura (ITP)" and is "not indicated for the treatment of thrombocytopenia in patients with chronic liver disease."<sup>17,18</sup>

On July 8, 2010, just weeks prior to the publication of the *Safety News* item regarding thrombosis with off-label use of eltrombopag, the FDA had issued a Risk Evaluation and Mitigation Strategy (REMS) warning against the off-label use of quinine sulfate (Qualaquin; URL Pharma) for nocturnal leg cramps or restless leg syndrome,<sup>19,20</sup> and a black box warning was added to the product label on August 3, 2010.<sup>21</sup> From April 2005 to October 1, 2008, the FDA received 38 reports of serious adverse events in patients treated with quinine sulfate, including "some" cases of permanent kidney impairment and 2 deaths. Reported adverse events included thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. Only 1 of the 38 patients was using the drug for its labeled indication, treatment of uncomplicated *Plasmodium falciparum* malaria.<sup>19,20</sup>

If these recent reports are any indication of what we can expect in the coming months, public concern about the safety of off-label drug use may grow, both in magnitude and in volume. If so, this trend may not be good news for those consumers and physicians who say that conflicts between the business interests of manufacturers and the FDA approval process diminish the prospects of drug approval, ultimately threatening the ability to treat catastrophic illness and "orphan" diseases.

### Public Concerns About Access to Care

Nearly concurrent with the publication of FDA and media reports about safety concerns regarding off-label use, actions

taken by the FDA and CMS raised public concerns about problems in access to care for rare and/or catastrophic diseases because of government-imposed labeling requirements and other restrictions on drug use.

### Midodrine for Orthostatic Hypotension

On August 16, 2010, the FDA recommended the withdrawal from the market of midodrine, an alpha-adrenoceptor stimulant, because "required post-approval studies that verify the clinical benefit of the drug have not been done."<sup>22,23</sup> Midodrine was approved by the FDA in September 1996 to treat orthostatic hypotension<sup>24,25</sup> under an abbreviated process called "accelerated approval."<sup>26</sup> Midodrine is unlikely to be noticed by managed care organizations because of its small patient population, estimated at only about 100,000 nationwide,<sup>27</sup> and relatively low cost. An unpublished analysis of one employer's data for pharmacy claims in mid-2010 found that midodrine was used by 1 patient for every 5,000 beneficiaries at an average price before copayment of approximately \$2.40 per day of therapy or about \$70 per month.<sup>28</sup> However, the FDA's proposed withdrawal of midodrine drew the attention of consumers and physicians because the conflict between the drug's 6 manufacturers and the FDA raised the possibility that none of the manufacturers would conduct the required post-approval studies.

In discussing the proposed market withdrawal of midodrine with a reporter, the FDA's Deputy Director for Clinical Science indicated that "for the same reasons we thought midodrine should be approved many years ago, we very much hope one of the sponsors... will conduct the studies needed to establish clinical benefit... and we do not believe the studies will be difficult."<sup>23</sup> But, the economics of a small patient population combined with competitive pricing among multiple manufacturers meant that 14 years after midodrine's initial approval, its original manufacturer (Shire) reported only about one-half million dollars annually from sales of the drug and was not inclined to fund the necessary studies, according to a representative in an interview reported on August 25, 2010: "We felt we had completed the postmarketing studies required, but the data that we submitted to FDA were deemed inconclusive, and [the agency] said we'd need additional data to show safety and efficacy... But we're not prepared to invest in more clinical trials at this time: from a business perspective, it doesn't make sense. From a consumer perspective, it would be better for the FDA to find a way to work this out."<sup>23</sup>

Because there are no other labeled indications for midodrine, if the FDA could not convince at least 1 of midodrine's 5 other manufacturers to fund the studies that it deems necessary, the product would have become unavailable for any use. However, after being "flooded" with complaints from patients, the FDA reversed its decision and announced on September 3, 2010, that midodrine could stay on the market for what a

spokesperson described as “the coming months.”<sup>27,29</sup> The FDA spokesperson noted that the legal requirement for additional studies “still stands, and we’ll continue with that formal process. The FDA plans to continue to allow access to the drug while the necessary data are collected and the legal issues get sorted out.”<sup>29</sup>

### Bevacizumab for Metastatic Breast Cancer

Described in an American Society of Clinical Oncology (ASCO) report in September 2010 as “potentially practice-changing news,” a highly publicized decision made by the FDA’s Oncology Drug Advisory Committee (ODAC) in July 2010 provided fuel for the fire for parties critical of the FDA, especially of the potential for its decision-making processes to restrict access to life-extending care.<sup>30</sup> The history of the FDA decisions regarding bevacizumab (Avastin; Roche-Genentech) warrants attention in a debate that has become emotionally and politically charged and potentially sets the stage for future FDA decisions.

Bevacizumab was granted accelerated approval status by the FDA in February 2008 for first-line treatment of metastatic human epidermal growth factor 2 (HER2)-negative breast cancer based on preliminary clinical trial data, despite a 5-to-4 vote by ODAC *against* this approval at its meeting on December 15, 2007.<sup>31</sup> The ODAC December 2007 decision was based on evaluation of the results of E2100, an open-label, multicenter, randomized trial of bevacizumab with paclitaxel versus paclitaxel alone in which the combination therapy was associated with an increase in progression-free survival (PFS) of 5.5 months (medians of 11.3 months for combination versus 5.8 months for paclitaxel alone,  $P < 0.001$ ) but no significant increase in overall survival (243 deaths [66.0%] in the combination group vs. 238 deaths [67.2%] for paclitaxel alone,  $P = 0.14$ ). The ODAC committee members expressed concerns at the time that included the E2100 trial’s open-label design, the toxicity of bevacizumab, shortcomings in safety data collection, and missing data that contributed to uncertainties in the effect size of PFS—creating the possibility that “patients could be offered false hope.” Committee members also agreed that although PFS is “a clinically meaningful endpoint,” it was unclear how best to measure PFS and concluded that overall survival must be included in evaluation of benefit versus risk.<sup>31</sup>

On July 20, 2010, the ODAC again voted against approval of bevacizumab for the indication of metastatic breast cancer, but this time in a more overwhelming vote of 12-to-1.<sup>32</sup> The second ODAC decision on bevacizumab was based on consideration of the results of 3 clinical trials of bevacizumab used first-line in patients who had not received previous chemotherapy for metastatic breast cancer, and the results of AVF 2119G, a trial that compared bevacizumab plus capecitabine with capecitabine alone in patients who had received previous chemotherapy.<sup>33</sup> AVF 2119G failed to demonstrate a statistically

significant effect of the addition of bevacizumab on either PFS or overall survival. In addition to E2100 for the first-line use of bevacizumab, 2 randomized controlled trials were presented that were “well-conducted, double-blinded trials, with less missing data compared to E2100.”<sup>31</sup> AVADO (BLA [biologics license application] 125085/191) and RIBBON1 (BLA 125085/192) were both conducted in samples of women with metastatic or locally recurrent breast cancer.<sup>32</sup> The results of AVADO and RIBBON1 were presented to the FDA by the manufacturer in an attempt to expand the indication to first-line therapy for metastatic breast cancer (in combination with docetaxel, anthracycline, or capecitabine) as well as to provide support for the conversion of the accelerated approval to regular approval;<sup>31</sup> the attempt appears to have been overly ambitious.

### Further Examination of the Evidence for Bevacizumab in Metastatic Breast Cancer

In AVADO, 736 women were randomly assigned to docetaxel plus placebo versus docetaxel plus bevacizumab 7.5 milligrams per kilogram (mg per kg) or 15 mg per kg every 3 weeks.<sup>34</sup> Testimony presented at the ODAC meeting by an FDA representative indicated that compared with placebo, bevacizumab 7.5 mg per kg “resulted in a 30 percent increase in [PFS], hazard ratio [HR]=0.7, with less than a month difference in median PFS,” and bevacizumab 15 mg per kg “resulted in a 39 percent increase in [PFS], [HR]=0.62, again, with less than a month difference in median PFS.”<sup>33</sup>

In RIBBON1, 1,237 women received either capecitabine ( $n=615$ ), taxane ( $n=307$ ), or anthracycline-based ( $n=315$ ) therapy, chosen by investigators. Within these cohorts, patients were randomly assigned to placebo or bevacizumab 15 mg per kg every 3 weeks.<sup>35</sup> FDA testimony about the RIBBON1 data indicated that compared with placebo, the addition of bevacizumab to taxane/anthracycline chemotherapy “resulted in a 30 percent increase in PFS, [HR]=0.64, with an observed 1.2 month difference in median PFS.” Again compared with placebo, the addition of bevacizumab to capecitabine “resulted in a 31 percent increase in PFS, [HR]=0.69, with an observed difference of 2.9 months in median PFS.”<sup>33</sup>

The improvements in median PFS in the AVADO and RIBBON1 trials were disappointing because they were lower than those reported in the E2100 trial (the basis for the FDA’s original accelerated approval designation).<sup>36</sup> An FDA representative noted in the ODAC meeting that the “initial enthusiasm” for potential approval of bevacizumab “resulted from a 52 percent increase in [PFS], [HR]=0.48, with an observed 5.5 month difference in median PFS observed when [bevacizumab] was added to paclitaxel.”<sup>33</sup>

The second ODAC decision is notable for 2 related reasons. First, the decision was based partly on rates of *overall survival*, not PFS alone. In AVADO, overall survival was not improved

with bevacizumab; median 30.8 months for 7.5 mg per kg plus docetaxel versus 31.9 months for placebo plus docetaxel (HR=1.10,  $P=0.483$ ), and median overall survival was 30.2 months in the 15 mg per kg arm (HR=1.00,  $P=0.983$ ).<sup>31</sup> In RIBBON1, overall survival was not improved in either the bevacizumab plus anthracycline/taxane cohort versus placebo plus anthracycline/taxane (HR=1.11,  $P=0.44$ ) or in the bevacizumab plus capecitabine cohort versus placebo plus capecitabine (HR=0.88,  $P=0.33$ ).<sup>31</sup> The decision was also based partly on increased rates of serious adverse effects associated with bevacizumab treatment, including hypertension, hemorrhage, wound healing complications, and febrile neutropenia.<sup>33</sup>

The second ODAC decision is also notable because it was based partly on a concern about the PFS measure: “FDA believes that in accepting PFS as a regulatory endpoint, a close examination of the magnitude of improvement in PFS must be closely evaluated in a risk-benefit analysis. Because the treatment with [bevacizumab] is associated with considerable toxicity, the magnitude of PFS improvement, especially if not supported by an improvement in overall survival, should be substantial, clinically meaningful, and be able to be replicated in additional trials.”<sup>33</sup> One commentary, written by a consultant to the manufacturer who “made a presentation in support of preserving and expanding the indications for bevacizumab” at the ODAC meeting on July 20, 2010, noted that the decision reflects a broader issue—lack of fundamental agreement on what an approvable indication is: “Genentech was asked in 2008 to perform confirmatory trials that showed improvements in PFS without decrements in survival. Most reasonable observers would say Genentech satisfied this requirement. However, ODAC then questioned the clinical significance of findings, without providing a definition of such. A situation in which sponsors and investigators must guess at the FDA’s wishes is not transparent or predictable and is therefore unfair. There is an urgent need for the FDA and the cancer community to agree upon exactly what qualifies a drug for approval.”<sup>37</sup>

### Implications of the Re-Evaluation of Bevacizumab for Metastatic Breast Cancer

Bevacizumab has other labeled indications and therefore will be available off-label if the FDA withdraws its approval of the breast cancer indication. However, critics of the ODAC recommendation have expressed concern that payers will be reluctant to cover an off-label indication for a drug with a direct provider acquisition cost of about \$7,700 per month or \$84,700 per 11-month course of treatment.<sup>38,39</sup> For some, the decision about bevacizumab was interpreted in light of the passage of the Affordable Care Act and the prospect of medical decisions being made by a government-run health care system.<sup>38,40</sup> These assessments unfortunately tended to focus primarily on the cost of bevacizumab, seeming to ignore or minimize the importance of overall survival and the adverse effects that

were weighed in the ODAC assessment. The United Kingdom’s National Institute for Health and Clinical Excellence (NICE) issued draft guidance on July 9, 2010, in which it rejected approval of the use of bevacizumab in combination with a taxane for metastatic breast cancer, citing “uncertain clinical benefit, combined with the amount of money the [National Health Service] is being asked to pay for the drug.”<sup>41</sup> NICE Chief Executive Andrew Dillon commented that, “There was also no proof that the drug can give patients a better quality of life than paclitaxel or docetaxel.”<sup>41</sup>

Critics of the ODAC decision on July 20, 2010, have also expressed concern about the use of overall averages to represent the results that could be attained for individual cases. For example, Nancy Brinker, the Chief Executive Officer of the Susan G. Komen for the Cure Foundation, noted that “we recognize the benefits of [bevacizumab] overall are modest for women with metastatic breast cancer. . . . However, we do know that for some women, [bevacizumab] offers a greater than modest benefit.”<sup>42</sup> Commenting on the possibility of CMS coverage denial of bevacizumab for metastatic breast cancer because of the FDA’s decision, Brinker, like the DOJ, sounded the theme of the importance of the doctor-patient relationship—but for a different purpose—to express *support* for off-label use: “the decision to use [bevacizumab] should be made *between a woman and her doctor* after a thoughtful conversation that carefully considers the drug’s benefits and risks. Komen does not want to see access limited by Medicare and Medicaid.”<sup>42</sup>

For private payers, the impact of the ODAC decision on reimbursement for the treatment of metastatic breast cancer with bevacizumab is not yet clear.<sup>43</sup> Key third-party payers emphasized in interviews with the *ASCO Post* that they intend to continue coverage of bevacizumab “for current responders” and to rely not only on the FDA, but also on the recommendations of the National Comprehensive Cancer Network Compendium, in their decision making.<sup>44</sup> However, as of 2008, only 3 of 6 cancer compendia included recommendations in favor of bevacizumab for breast cancer.<sup>45</sup> Additionally, a 2009 systematic review by Abernethy et al. suggested substantial problems in the consistency and accuracy of compendia, noting that they “lack transparency, cite little current evidence, and lack systematic methods to review or update evidence.”<sup>45</sup> Thus, the future use of compendia by public and private payers is uncertain.<sup>46</sup>

### ■ Inconsistencies in CMS Reimbursement Policies for Off-Label Use

A look at the recent history of reimbursement policy controversies and legislative proposals for Medicare and Medicaid reveals an unwieldy patchwork that has sometimes confused or even angered stakeholders.

### About-Face on Off-Label Use of Bevacizumab for Age-Related Macular Degeneration

On October 9, 2009, the Chair of the U.S. Senate Special Committee on Aging, Herb Kohl, wrote to CMS to *support* an off-label indication, using language suggesting product effectiveness that had actually not yet been adjudicated by the FDA. The letter expressed the committee's "serious concern about the... recent change in reimbursement coding rules for a widely-used, *highly effective*, and modestly priced treatment for age-related macular degeneration (AMD)," a compounded form of bevacizumab administered off-label within "the ophthalmologic and retinal specialist communities" by "at least half of their members nationwide."<sup>47</sup> (emphasis added) The letter followed a 2-year controversy that began when the manufacturer of *both* bevacizumab and ranibizumab (Lucentis), an injectable that is FDA-approved for neovascular ("wet") AMD, announced in October 2007 its intention to make bevacizumab unavailable to compounding pharmacies and reportedly refused to cooperate with a head-to-head trial of the 2 drugs conducted by the National Institutes of Health.<sup>48</sup> The stated rationale for the manufacturer's decision included several factors: availability of a drug approved for the indication; the smaller molecule size of ranibizumab, specifically designed for retinal penetration; and concern about whether the trial's sample size would be sufficiently large to assess rare side effects.<sup>49</sup> According to a manufacturer spokesperson interviewed in August 2008, "no matter the outcome [of the trial], we continue to believe [ranibizumab] is the most appropriate treatment for wet AMD. ... Our resources would be better spent looking at other diseases where there are no treatments."<sup>49</sup>

Effective October 1, 2009, CMS promulgated for the first time a specific reimbursement code for use of bevacizumab to treat AMD based on "a formula that is determined by law, and doesn't take into account the costs of repackaging the drug," effectively reducing the approximate reimbursement to physicians for a bevacizumab injection for AMD from \$50 to \$7, compared with reimbursement of \$2,039 for ranibizumab.<sup>50</sup> Because approximate acquisition costs were \$27 (paid to compounding pharmacies) for bevacizumab and \$2,000 for ranibizumab, the code change essentially penalized physicians for using bevacizumab off-label. After Kohl alleged improper influence of the manufacturer over CMS and expressed concerns about patient copayments and the estimated cost of up to \$3 billion to Medicare for ranibizumab,<sup>47</sup> the CMS announced on October 28, 2009, the reversal of its coding decision effective January 1, 2010.<sup>51</sup>

Commenting in June 2010 on the leaking of a study suggesting that CMS could save the federal government "millions... by more aggressively reimbursing for" bevacizumab used off-label for AMD, the Washington Legal Foundation (WLF) argued that the CMS actions appeared to be "motivated by cost savings rather than patient care." Observing that the

FDA had "shut down most communication about off-label uses between health product companies and physicians" with the "punishing support" of the DOJ, Glenn Lammi, Chief Counsel of the WLF Legal Studies Division, argued that government actions reflected a "double-standard."<sup>52</sup>

### Inconsistent Reimbursement for Off-Label Use of Anticancer Drugs Within Medicare

The use of bevacizumab for ovarian cancer, another off-label use, became the subject of a Medicare coverage controversy just a few days before resolution of the AMD dispute. On October 23, 2009, a bipartisan group of 30 congressional representatives led by Betsy Markey (Colorado) sent a letter to CMS and TrailBlazer Health Enterprises, the Medicare Administrative Contractor for Part A and Part B coverage in 4 states (Colorado, New Mexico, Oklahoma, and Texas),<sup>53</sup> pointing out that off-label use of bevacizumab for ovarian cancer was covered in "at least 29 other states" but not in states under TrailBlazer's jurisdiction.<sup>54</sup> The inconsistency occurred, the letter noted, because "CMS guidance gives the contractor wide discretion for off-label uses and TrailBlazer Health has denied this use based on a non-supportive indication in a single pharmaceutical compendium." Like the Kohl letter supporting off-label use of compounded bevacizumab for AMD, the Markey et al. letter invoked terminology that would typically describe an FDA-approved indication, noting that 3 of 4 "accepted pharmaceutical compendia and numerous clinical studies support [bevacizumab] as a *safe and effective* treatment for ovarian cancer."<sup>54</sup> (emphasis added)

### Proposals to Expand Off-Label Coverage in Medicare Compete with Proposals to Restrict It

The Markey et al. letter was followed 9 months later on July 15, 2010, by the introduction of a bipartisan bill by Mary Jo Kilroy (Ohio) and Mac Thornberry (Texas) to "eliminate the current prohibition on Part D plans covering non-cancer off-label drugs" when off-label drug use is supported by "authoritative medical literature," the standard currently applied to drugs covered under Part B.<sup>55</sup> In language again reminiscent of the FDA's mandate despite advancing a proposal to *expand* off-label use, proponents of the "Part D Off-Label Prescription Parity Act" argued that the bill, which "has the strong backing of the National Multiple Sclerosis Society," will grant "all Medicare consumers access to *safe and effective* prescription treatments, regardless of the condition from which they suffer."<sup>55</sup> (emphasis added)

Yet, patient safety is likely to be a major factor in another CMS debate about whether to *curtail* coverage of a product that is frequently used off-label. At this writing, BMP-2, the subject of August 2010 news reports on the potential dangers of off-label use,<sup>14</sup> is slated for discussion in a September 22, 2010 meeting of the Medicare Evidence Development & Coverage

Advisory Committee (MEDCAC) to “consider the currently available evidence regarding the clinical benefits and harms of on-label and off-label use of BMPs.”<sup>56</sup> The MEDCAC meeting announcement indicated that the committee will address “clinically meaningful health outcomes of interest” including “pain, patient function and adverse events related to” both on-label and off-label use of BMPs; the off-label uses to be discussed include cervical spine, lumbar spine, and others.<sup>56</sup>

### “Safe and Effective” Versus “Reasonable and Necessary”: CMS Coverage Uncertainty Expands to On-Label Use of Expensive Drugs

Medicare coverage of the *on-label* use of an injectable therapy, sipuleucel-T (Provenge; Dendreon), which was FDA-approved for the treatment of metastatic hormone-refractory prostate cancer on April 29, 2010,<sup>57</sup> came into question when the CMS announced in July 2010 that it would take a year to determine its reimbursement policy for the drug.<sup>58</sup> The 1-year process will include an initial 1-month public comment period, 9 months of study and an initial proposal by the MEDCAC, followed by a second public comment period and a final decision anticipated in June 2011.<sup>59</sup> Pending the CMS decision, regional Medicare carriers can make independent coverage determinations about sipuleucel-T.<sup>58</sup>

An observer writing for the *Wall Street Journal* health blog pointed out that the CMS decision potentially represented a major policy shift. “It’s worth noting that despite the chatter over the price of the drug—\$93,000 for a course of infusions—CMS is not supposed to consider that factor.”<sup>58</sup> The CMS guidance for factors to be considered in opening a National Coverage Determination (NCD) includes the following: “Cost effectiveness is not a factor CMS considers in making NCDs. In other words, the cost of a particular technology is not relevant in the determination of whether the technology improves health outcomes or should be covered for the Medicare population through an NCD.”<sup>60</sup>

Similar concerns about the Medicare coverage determination process were expressed in an August 2010 *San Francisco Examiner* editorial, which observed that Donald Berwick, the newly appointed CMS administrator, was facing “life-and-death choices” about coverage of expensive anticancer drugs including sipuleucel-T used on-label for prostate cancer.<sup>61</sup> The issue, as reported to the *Examiner* by the Ovarian Cancer National Alliance (OCNA), is a discrepancy in the criteria for FDA approval (“safe and effective”) and Medicare coverage (“reasonable and necessary”). In considering sipuleucel-T, the OCNA observed, “it appears that [CMS] is arguing that while the treatment is safe and effective, it may not be reasonable and necessary. For the first time, an FDA-approved anti-cancer therapy may not be covered by Medicare.”<sup>61</sup>

Notably, sipuleucel-T delivers increased overall survival of only about 4.1 months on average—median survival of 25.8

months for patients treated with sipuleucel-T versus 21.7 months for those receiving placebo in the clinical trial used by the FDA in making its approval decision.<sup>57</sup>

### Alternative Proposals for Coverage of Off-Label Use

Several proposals to balance the sometimes competing interests that come into play in off-label drug prescribing—patient safety, patient preferences, need for effective therapies, physician autonomy in medical decision making, and affordability of coverage—merit examination. First, to address situations like that of midodrine, editorialists Liang and Mackey proposed in January 2010 an enhancement to the 1983 Orphan Drug Act that would create a process by which drugs could be marketed and used off-label in clinical practice for orphan diseases, defined in the United States as conditions affecting less than 200,000 patients.<sup>62</sup> Their proposed process includes an application in which manufacturers would provide information about the rare disease to be treated, including prevalence, regulatory and marketing status and history; available drug safety and efficacy data; a pharmacovigilance plan for monitoring to include reporting of adverse effects and a “mandated efficacy assessment (after a defined time, based on the specific drug);” submission of promotional materials to the FDA for approval prior to marketing; and “attestation that promotion would not be false or misleading.” Submission of “fraudulent materials” would subject the manufacturer to “federal fraud claims and patient tort suits” in the event of patient injury. If the patient base exceeded a threshold, perhaps 4,000 patients, which is the number of patients “often required for standard FDA drug approval,” the manufacturer would be required to file a supplemental new drug application.<sup>62</sup>

In principle, the proposal by Liang and Mackey is similar to the “coverage with evidence development” (CED) process used sporadically by CMS since 1995, formalized in 2005, for a limited number of diagnostic procedures and treatments, such as implantable cardioverter defibrillators and positron emission tomography (PET) scanning for certain malignancies and for dementia and neurodegenerative diseases.<sup>63,64</sup> Under CED, an NCD for Medicare requires, “as a condition of coverage, collection of additional patient data to supplement standard claims data.”<sup>63</sup> CED can be used to address questions either about appropriateness of use (i.e., “coverage with appropriateness determination”) or effectiveness and safety of use (“coverage with study participation”).<sup>64</sup> Originally intended to “reduce the logjam between innovation and evidence-based coverage policy”<sup>64</sup> by requiring patient participation in a clinical trial or observational study as a condition of coverage, CED has been proposed as a potential solution to the problem of “financial burden on product development that is associated with conducting new studies” to support additional FDA-approved indications for anticancer drugs.<sup>46</sup>

Informed consent, among the recommendations described

in Zheng and Xu's letter in this issue of *JMCP*, has been proposed elsewhere because "providing full disclosure to patients and encouraging them to share in decision-making in situations of medical uncertainty is vital to respecting their autonomy."<sup>65</sup> However, a thoughtful editorial by Gillick (2009) observed that obtaining "meaningful informed consent" is problematic "when few or no data on benefit are available," as in many circumstances in which drugs are used off-label.<sup>66</sup> Gillick also dismisses proposals for a centralized federally sponsored prior authorization process as "creating enormous bureaucratic obstacles to access."<sup>66</sup>

Gillick's creative proposal to address the dual problems of threats to patient safety and potentially wasteful expenditure on drugs not efficacious for off-label indications is to implement something like the NCD process that is currently used by CMS for determination of Medicare coverage for medical devices.<sup>67</sup> Specifically, Gillick's proposed process would focus primarily on drugs that "are both risky and expensive" because "in practice, the most expensive medications are often those with the greatest risk for toxicity." Gillick proposes that an appropriate cost threshold to trigger an NDC review of an off-label medication use would be \$12,000 annually, equivalent to the one-time average cost to CMS for insertion of a single-chamber pacemaker (suggested as a benchmark because pacemakers are "typical," i.e., commonly used). Once triggered, the NCD would be carried out using CMS' usual coverage determination process, which Gillick describes as both evidence-based and transparent. Gillick argues that in making their coverage determinations, private payers might follow the lead of CMS.<sup>68</sup>

### ■ The Future of Off-Label Drug Use—What's Next?

Putting aside the technical merits of specific proposals, it is important to consider the roles that public opinion, press coverage, and ethical considerations will play in making any determination on off-label use. As Tunis and Pearson observed in their 2006 commentary on CED, the "tension between the promise of technology and the perceived burden of evidence-based coverage" is "particularly vivid" for some treatments, such as biologic treatments for cancer.<sup>64</sup> Gillick similarly pointed out that "health insurers are so afraid of negative publicity from advocacy groups, as well as possible lawsuits on behalf of patients with cancer, that they rarely restrict access to new chemotherapeutic agents."<sup>66</sup> Thus, actions that have the effect of restricting access—either by withdrawing or denying FDA approval for a specific indication or by limiting public or private insurance coverage—are likely to be met with public opposition. As Tunis and Pearson pointed out, "intense public reaction" followed the application of CED by CMS to coverage of colorectal cancer treatment with biologic drugs used off-label.<sup>64</sup>

Moreover, in the face of uncertain evidence about treatment efficacy, especially about which patient subgroups are likely

to experience results better than the medians often used in drug approval decisions, restricting or denying coverage for physician-recommended treatments requires a careful and transparent airing of ethical considerations. These considerations should include efficacy and safety results overall and for different patient subgroups, as well as a frank acknowledgment of limitations in the evidence base and willingness to reconsider or modify coverage as evidence accumulates over time. For example, in 1995 CMS (then named the Health Care Financing Administration) applied a CED-type process to Medicare coverage of lung volume reduction surgery (LVRS) for patients with severe emphysema, a procedure for which there was at the time "enthusiastic adoption ... in the absence of well-designed trials."<sup>64</sup> The resulting study, the National Emphysema Treatment Trial (NETT), identified a subgroup of patients who were more likely to benefit from, and less likely to be harmed by, use of LVRS. The result was a modification of the Medicare NCD "to cover all patients who matched the characteristics of patients in the trial" who "achieved a slightly better quality of life or a small survival benefit" from the surgery.<sup>64</sup> Tunis and Pearson observed that if Medicare coverage had been granted without the NETT, "the true benefits and risks of LVRS would have remained unknown, thereby subjecting thousands of beneficiaries to unnecessary risks." However, ethical concerns have also been raised about CED itself, that is, whether requiring participation in a trial to obtain coverage constitutes coercion.<sup>64</sup>

In the present debate, core values in health care—such as patient safety, access to the most effective treatments, and preservation of the doctor-patient relationship—are being cited as justification *both* for expansion *and* curtailing of off-label drug use. The current tangled web of conflicting public opinions, equally conflicting reimbursement policies and proposals, and rapid development of potentially life-saving or life-extending pharmaceutical technology does not provide a foundation for quick or easy resolution. And, the debate is typically spirited and even vehement. It is perhaps a sign of the times that in researching consumer and advocacy group opinions about off-label use in the popular press, we had difficulty finding source material that did not include personal name-calling directed against decision makers.

Viewed in a broader context, as we observed in the November/December 2009 issue of *JMCP*, vociferous conflicts such as that currently ongoing over off-label use are a predictable outgrowth of unrealistic expectations that any health care system can simultaneously cover 100% of the cost of preventive care, including the expansion of pharmacotherapy for primary prevention to tens of millions of Americans annually; pay for unrestricted access to any and all therapies regardless of expense, safety, or efficacy; allow open season litigation against health plans for every coverage denial; continue to pay providers at prevailing market rates; *and* reduce *both* enrollee

out-of-pocket and total health care costs.<sup>68</sup> Off-label drug use is just one aspect of the larger question about how to balance benefits, harms, and costs of medical interventions when technological advances are rapid, evidence is imperfect, and resources are finite.

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## DISCLOSURES

The authors report no conflicts of interest related to the subjects or products discussed in this article.

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