Consider the Evidence: CMS and DOJ at Odds Over the Role of Scientific Data in Medicare Drug Reimbursement Determinations

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On the heels of a Food and Drug Administration (FDA) advisory committee’s recommendation that Avastin no longer be indicated for the treatment of breast cancer, the Center for Medicare and Medicaid Services (CMS) nevertheless announced that Medicare will continue to pay for such use. CMS’ announcement confirms what drug manufacturers have long argued in the context of civil False Claims Act (FCA) litigation involving claims for “off-label promotion”: Medicare coverage is not driven by FDA approval, but rather is—and should be—based upon physicians’ professional determinations that a given drug is “reasonable and necessary” for use by a particular patient for a specific indication. CMS’ decision to continue to provide reimbursement for breast cancer patients using Avastin also stands in contrast to legal and policy positions adopted by the Department of Justice (DOJ) in FCA cases involving promotional practices.

FDA Considers Revoking Avastin’s Approval for Breast Cancer

Avastin (bevacizumab) is an injectable cancer medication manufactured and marketed by Genentech. Avastin blocks a
protein that is important for the formation of blood vessels and is thought to work by preventing the formation of new blood vessels that feed cancer tumors.\(^1\) Avastin was first approved in 2004 for treatment of advanced colon cancer and has since been approved for advanced lung cancer in 2006, and for kidney and brain cancers in 2009. In 2008, Avastin was approved for metastatic breast cancer under FDA’s accelerated approval program, which permits the approval of a drug based on results of clinical data that suggest the drug has an important clinical benefit.\(^2\)

Under the accelerated approval program, however, additional information is needed to confirm the data. In particular, fast track products may be approved, as Avastin was, with a requirement that the drug sponsor conduct appropriate post-approval studies to validate the data supporting the accelerated approval.\(^3\) If a post-approval study of a fast track product fails to verify the clinical benefit of the product, FDA may withdraw approval of the fast track product using expedited procedures.\(^4\)

In December 2010, FDA announced that the agency’s Center for Drug Evaluation and Research (CDER) was proposing to withdraw Avastin’s indication for metastatic breast cancer, based on a finding that there was not enough evidence that the drug is safe and effective for the breast cancer indication.\(^5\) On June 28 and 29, 2011, FDA held a public hearing on CDER’s proposal, during which the agency’s Oncologic Drugs Advisory Committee recommended that FDA withdraw its approval of Avastin in combination with paclitaxel chemotherapy for previously untreated (first-line) HER2-negative metastatic breast cancer.\(^6\)

FDA’s decision is not yet final; CDER and Genentech provided additional written submissions on August 4, 2011, and the docket remained open for public comment until that date.\(^7\) FDA Commissioner Dr. Margaret Hamburg will now make a final decision on Avastin’s approval for use in treating metastatic breast cancer.\(^8\) Commissioner Hamburg’s decision will not affect Avastin’s approved indications for use in colon, lung, kidney, and brain cancers, and Avastin will remain on the market. As a result, physicians will be free to prescribe Avastin off-label for metastatic breast cancer.

**CMS Announces That It Will Continue to Cover Avastin**

Following FDA’s June 2011 public hearing, CMS announced that the agency would continue to pay for Avastin when used to treat breast cancer, even if FDA revokes the drug’s approval as a treatment for the disease.\(^9\) According to a CMS spokesperson: “The FDA decision, when it comes, does not affect CMS.”\(^10\) The spokesperson explained that “[t]he drug will still be on the market, doctors will still be prescribing it, and [CMS] will continue to pay for it,” adding that CMS often pays for off-label uses of drugs.\(^11\)

**CMS’ Position Inherently Conflicts With DOJ’s Position In Recent FCA Investigations and Litigation**

CMS’ assertion that Medicare will continue to cover Avastin regardless of FDA’s decision—and regardless of an FDA finding that there is insufficient scientific evidence to support Avastin’s use in breast cancer—confirms that neither of these factors is dispositive of whether the use is medically “reasonable and necessary,” i.e., eligible for Medicare coverage by statute.\(^12\) CMS’ position is consistent with the argument that pharmaceutical and medical device companies have long made (with limited success) in FCA investigations and litigation: that neither the off-label status of a particular use nor the quantum of scientific support for that use determines whether the use is properly reimbursable under Medicare’s “reasonable and necessary” standard. Accordingly, the absence of FDA approval or specific scientific evidence supporting a particular use does not establish that those claims are “false” for purposes of FCA liability.

This argument goes to the very heart of the Government’s and *qui tam* relators’ ability to state—and prove—a claim under the FCA. That statute prohibits, in relevant part, “knowingly present[ing], or caus[ing] to be presented, a false or fraudulent claim for payment or approval.”\(^13\) If a particular claim for Medicare reimbursement is neither false nor fraudulent, it cannot provide the predicate for an FCA violation.

DOJ, however, has opposed this argument when raised by FCA defendants. For instance, in *United States ex rel. Strom v. Scios, Inc.*,\(^14\) DOJ alleged that Scios, Inc. violated the FCA by promoting the drug Natrecor for use in serial, scheduled outpatient infusions when Natrecor was only approved by FDA for intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.\(^15\) DOJ alleged that during the period at issue, “serial, scheduled outpatient infusions of Natrecor were not eligible for payment by Medicare because this off-label use was neither ‘reasonable and necessary,’ nor ‘medically accepted.’”\(^16\) According to DOJ, the use failed to meet Medicare’s statutory standard because “the use was not supported by any credible study showing that the serial outpatient infusions were effective.”\(^17\) DOJ alleged the claims were “false because the off-label use is not covered” by Medicare.\(^18\)
Scios argued that even if Scios’s clinical trials failed to demonstrate the efficacy of Natrecor for outpatient infusions, lack of proof of efficacy does not establish falsehood. . . . this situation is endemic to off-label use; almost by definition, a use is off-label precisely because there is insufficient evidence to support its approval by the FDA. If the mere lack of conclusive evidence were sufficient to establish falsity, there would be no such thing as a legitimate off-label claim—much less a regulatory framework in which off-label uses are an “accepted aspect of a physician’s prescribing regimen.”

Scios further argued that the scenario described in the Complaint is typical of the off-label context: “lacking data from a Phase III, double-blinded, placebo-controlled clinical trial, 4,000 physicians nonetheless determined—more than 170,000 times, based on their own first-hand observations of patients’ actual responses to the drug—that serial infusions of Natrecor were reasonable and necessary for the treatment of chronic heart failure.” This argument espoused the principle that CMS appears to have embraced in its recent announcement regarding Avastin coverage: individual physician judgments determine whether particular uses are “reasonable and necessary.”

Nevertheless, the court rejected Scios’s argument that DOJ’s Complaint failed to allege the falsity required for a False Claims Act case. The court glossed over Scios’s arguments, finding that “[b]ecause the [Medicare] statute permits reimbursement only for ‘reasonable and necessary’ treatments . . . a prescription of Natrecor in a context where it is not ‘reasonable’ or ‘necessary’ would be statutorily ineligible for reimbursement. This satisfies the FCA’s requirement of a ‘false’ statement.” In reaching this conclusion, the court appears to have relied, at least in part, on the Government’s allegations that Scios overstated the nature of the available scientific evidence to the physicians who prescribed Natrecor for outpatient infusions. DOJ’s briefs in Strom, however, do not rely on any alleged misrepresentations on the part of Scios. Rather, DOJ argues that the alleged lack of scientific evidence, in and of itself, means that claims for Natrecor for outpatient infusion could not have been “reasonable and necessary” and therefore were not eligible for reimbursement by Medicare.

CMS’ announcement regarding Avastin, however, highlights the flaw in DOJ’s theory: neither FDA approval nor the quantum of available scientific evidence, in isolation, determines Medicare coverage.

DOJ’s Position Overlooks the Key Role of Physicians

DOJ’s briefs in Strom improperly ignore the central role that physicians and other health care providers play in determining whether the specific use of a given drug or medical device is “reasonable and necessary” for an individual patient, based upon each patient’s unique circumstances. Under Medicare’s reimbursement scheme, however (and as CMS’ announcement regarding Avastin confirms), that determination does, and should, control.

Indeed, the U.S. District Court for the Southern District of Texas recently recognized this principle in two FCA cases involving allegations of off-label promotion by two medical device manufacturers. In U.S. ex rel Bennett v. Boston Scientific Corporation and U.S. ex rel. Bennett v. Medtronic, Inc., a qui tam relator alleged that medical device manufacturers unlawfully promoted the use of surgical ablation devices to treat atrial fibrillation. The relator further asserted that the defendants’ alleged off-label promotion “caused physicians and hospitals to submit claims to the government falsely stating that the use of the [devices at issue] was ‘reasonable and necessary’ or ‘medically necessary,’” but that the use of the surgical ablation devices to treat atrial fibrillation could not be medically necessary because the device was not FDA approved for such use. In separate opinions, the court granted the defendants’ motions to dismiss, finding among other things that “[t]he decision on medical necessity is made by individual physicians exercising independent professional judgment based on the knowledge of their particular patients. The cases recognize that off-label use of a drug or medical device is distinct from a medically unnecessary use of that drug or device.”

While scientific evidence (or the lack thereof) may be determinative in certain instances, in others, a physician may decide that a particular off-label use of a medical device or drug is reasonable and necessary based upon his or her own observations or based on conversations with other physicians. In either case, the physician’s determination controls whether the use is reimbursable under Medicare.

DOJ’s Wrongful Theory Has Significant Impact for FCA Defendants

DOJ’s failure to respect and follow CMS’ policy as to how coverage determinations are made is more than an interesting intellectual inconsistency. Because DOJ is responsible for litigating FCA cases and prosecuting criminal off-label promotion cases, DOJ’s flawed theory has a real and substantial impact for pharmaceutical and medical device manufacturers.
In particular, because the FCA provides for both treble damages and statutory penalties for each false claim allegedly presented, DOJ possesses enormous leverage to demand settlements reaching into the millions, and sometimes billions, of dollars in cases involving alleged off-label promotion. DOJ’s financial threats are coupled with the potential for exclusion from participation in federal health care programs as well as FDA debarment. These pressures frequently force pharmaceutical and medical device manufacturer defendants to settle FCA cases in order to resolve claims that they have committed “fraud” against the federal government by allegedly promoting their products for uses that are not approved by FDA.

DOJ, both in legal briefs and in public statements, frequently equates alleged off-label promotion with fraud, without identifying allegedly false or misleading actions on the part of manufacturer defendants. CMS’ recent announcement regarding Avastin, however, underscores that Medicare coverage turns on a particular physician’s determination, in his or her independent medical judgment, that a specific use is “reasonable and necessary” for a given patient. Viewed in this light, it is clear that claims for Medicare reimbursement are not “false or fraudulent” simply because FDA has not found sufficient scientific evidence to approve the underlying use. Much to the contrary, it is inherently unjust for DOJ—in its role as the FCA enforcement agency—to continue to claim that manufacturers are committing “fraud” when its sister agency, CMS, knowingly pays for the off-label use underlying an FCA enforcement action. △

3. Id. § 356(b)(2)(A).
4. Id. § 356(b)(3).
6. Id. at 204-268.
7. See FDA, Avastin Information. The public docket is available at http://www.regulations.gov/#/SearchResults; rpp=1;so=DESC;sb=postedDate;po=0;sl=avastin (last visited Sep. 23, 2011).
8. At the time of publication, Commissioner Hamburg had not made a decision as to whether to withdraw Avastin’s approval for use in treating breast cancer and neither the timing of her decision nor the likely outcome were known.
11. Id.
12. See 42 U.S.C. §§ 1395y(a)(1)(A) (“Notwithstanding any other provision of this subchapter, no payment may be made under [Medicare Part A or Part B (which covers drugs that are provided incident to a physician’s services)] for any expenses incurred for items or services—(i) which . . . are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member . . . .”). While this is the extent of CMS’ express statutory authority, the Medicare Benefit Policy Manual also explains that “FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice. . . .” Medicare Benefit Policy Manual, Chap. 15 § 50.4.2.
16. Id. ¶ 105.
17. Id.DOI’s Complaint also alleged that Natrecor was not “medically accepted” (i.e., did not meet the standard described in the Medicare Benefit Policy Manual). U.S. Compl. ¶ 105. In opposing Scios’ Motion to Dismiss the Complaint, however, DOJ relied primarily upon the alleged lack of scientific evidence of Natrecor’s efficacy for outpatient infusions. See U.S. Mem. in Opp’n toDefs’ Mot. to Dismiss at 5-7 ("serial outpatient infusions are not only off-label but are also medically unnecessary and thus are ineligible for payment under Medicare. . . . As alleged in the Complaint, neither of Defendants’ outpatient FUSION studies demonstrated efficacy of the serial infusions. No other sound clinical evidence exists supporting the outpatient use of Natrecor.” (citing U.S. Compl. ¶¶ 48-51, 53-54, 105, 111-113)).
18. U.S. Compl. ¶ 114.
20. Id. at 6.
22. Id. at 891 n. 2 (rejecting Defendants’ suggestion that the Government’s Complaint would require the Court to “second-guess doctors’ considered medical opinions” (quoting Scios Mot. to Dismiss at 10)).
23. See supra note 15.
26. Id.
27. As the Bennett cases explain in detail, CMS regulations distinguish between certain types of medical devices with respect to the reimbursability of off-label use.See Bennett v. Medtronic, 747 F. Supp. 2d at 752-54. For both medical devices and drugs, however,
the underlying statutory authority is based upon the reasonable and necessary standard. Id.; 42 U.S.C. § 1395y(a)(1). Indeed, on October 5, 2011, Scios pled guilty to a misdemeanor violation of the FDCA relating to the promotion of Natrecor for use in serial, scheduled outpatient infusions. Pursuant to the plea agreement between Scios and the United States, the company agreed to pay an $85 million criminal fine. Although this settlement resolves Scios’s criminal FDCA liability relating to the off-label promotion of Natrecor, the civil FCA case—alleging that Scios’s off-label promotion caused the submission of false claims—remains active.

29. Although CMS’ announcement regarding Avastin confirms important limitations with respect to manufacturers’ FCA liability, it should be noted that a violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (FDCA) may nevertheless lie where a manufacturer allegedly promotes a product for an off-label use, regardless of whether that alleged promotion led to any CMS reimbursement. Indeed, on October 5, 2011, Scios pled guilty to a misdemeanor violation of the FDCA relating to the promotion of Natrecor for use in serial, scheduled outpatient infusions. Pursuant to the plea agreement between Scios and the United States, the company agreed to pay an $85 million criminal fine. Although this settlement resolves Scios’s criminal FDCA liability relating to the off-label promotion of Natrecor, the civil FCA case—alleging that Scios’s off-label promotion caused the submission of false claims—remains active.

31. CMS’ confirmation that its coverage decisions do not turn on FDA approval also has implications beyond FCA cases involving a drug’s efficacy for a particular indication. In instances where FDA requires a pharmaceutical manufacturer to change a product’s label to provide additional warnings or to strengthen existing warnings, that manufacturer often faces follow-on litigation by insurers seeking to recover amounts paid for prescriptions prior to the label change. Insurers whose reimbursement policies follow CMS’ guidelines, such as supplemental Medicare providers, argue that, had the new safety information been provided earlier, CMS would not have reimbursed for the drug and they, therefore, would not have done so either. CMS’ recent announcement regarding Avastin, however, undermines this position. In light of CMS’ announcement, plaintiffs pursuing this theory must show causation through remote links in a chain and speculation as to how a government agency would exercise its discretion. Cf. United Food & Commercial Workers Cent. Pa. & Reg’l Health & Welfare Fund v. Amgen, Inc., 400 Fed. App’x 255, 257 (9th Cir. 2010) (holding that plaintiffs’ alleged causal chain was too attenuated where it depended on several links, including Medicare’s decision to cover Aranesp for anemia of cancer).