

[DO NOT PUBLISH]

IN THE UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

Nos. 14-15342 & 15-12005
Non-Argument Calendar

D.C. Docket No. 1:13-cv-22782-MGC

VITREO RETINAL CONSULTANTS OF THE PALM BEACHES, P.A.,
a Florida corporation,

Plaintiff - Appellant,

versus

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES,

Defendant - Appellee.

Appeals from the United States District Court
for the Southern District of Florida

(April 29, 2016)

Before HULL, MARCUS, and ROSENBAUM, Circuit Judges.

PER CURIAM:

Plaintiff-Appellant Vitreo Retinal Consultants of the Palm Beaches, P.A. (“VRC”), brought suit in the Southern District of Florida against the United States Department of Health and Human Services (“HHS”) and the Secretary of HHS Sylvia Burwell (“Secretary”) seeking the recoupment of payments VRC returned to Medicare after it was issued notice of an overpayment. Throughout the Medicare administrative review process, HHS upheld the ruling denying recoupment. The district court similarly affirmed HHS’s decision. After careful review, we now affirm the ruling of the district court upholding the administrative decision.

I.

A. Administration of Lucentis

During the years 2007 and 2008, VRC served patients covered by Medicare Part B who suffered from age-related macular degeneration (“AMD”) and other retinal diseases. Among other treatment methods for AMD, VRC administered the intravitreal injection of Lucentis. Lucentis is FDA approved for the treatment of AMD. It is manufactured and sold by Genentech, Inc., in 2.0-mg vials.

The FDA-approved labeling on the drug instructs that a single 0.5-mg dose of Lucentis be injected into the patient’s eye once each month. The proper method for extracting the drug and administering the injection described on the label requires the healthcare professional to extract the *full contents* of the 2.0-mg vial

into a syringe. The contents of the syringe are then to be expelled until the plunger tip is aligned with the line that marks 0.05 mL (0.5 mg). Then the dose is to be injected into the patient's eye. The label further instructs that “[e]ach vial should only be used for the treatment of a single eye.”

First Coast Service Options, Inc., administers Medicare payment processing in Florida. SafeGuard Services LLC audits Medicare claims. In February 2008, First Coast issued its first Local Coverage Determination for Lucentis, acknowledging that the drug was “medically reasonable and necessary” for the treatment of AMD. The Local Coverage Determination incorporated the label’s instruction that “[e]ach vial should only be used for treatment of a single eye.”

VRC did not follow the Lucentis label’s instructions limiting dosage to one per vial. Instead, VRC treated up to three patients from a single vial. It did so by extracting up to three doses of 0.5 mg each from one vial into three separate syringes. This process is referred to by the parties as “multi-dosing.” VRC billed Medicare for every 0.5-mg dose of Lucentis it administered.

The reimbursement rate for Medicare Part B drugs is capped at the lower of the physician’s billed charge or 106% of the drug’s average sales price. 42 U.S.C. § 1395w-3a. The drug’s average sales price, in turn, is calculated quarterly based on nationwide sales, divided by the total number of units of drug sold. *Id.* (c)(1), (5)(B). Physicians receive reimbursement based on the number of dosage units

used to treat a patient. *Id.* (b)(1). Where a drug's administration results in wasted contents, Medicare reimburses the physician for the waste if it was a necessary part of administration. Medicare Claims Processing Manual, Pub. No. 100-04, Ch. 17, § 40.

The calculated reimbursement rate of Lucentis during the period at issue was approximately \$405 per 0.1 mg administered or \$2,025 for a standard 0.5-mg dose.¹ This price was reached by determining the cost of an entire single-use vial of Lucentis. The average sales price for a vial was \$2,025. This price was then assigned as the cost of one dose of 0.5 mg. The 0.5-mg dose was then broken down into individual units of 0.1 mg, with a reimbursement rate of \$405 ($\$2,025 \div 5$). Hence, if administered according to the label, a provider would inject 0.5 mg into a patient's eye, dispose of 1.5 mg, and receive reimbursement in the amount of approximately \$2,025 for the single vial—or the total average cost of the 20-mg vial. VRC billed Medicare at the allowed rate for every 0.5-mg dose it administered,² resulting in a bill for approximately \$2,025 for every dose. Because VRC was extracting up to three doses from a single vial, it was “reimbursed” for approximately \$6,075 per single Lucentis vial, three times the average cost of the

¹ During 2007-2009 the average sales price of Lucentis fluctuated between approximately \$405 and \$407. The exact amount is immaterial for the purpose of this opinion.

² VRC's billed charge was higher than the 106% statutory rate, so the lower rate based on the average sales price was applied in accordance with the Medicare statute. 42 U.S.C. § 1395w-3a.

vial and three times the amount it would have received had it administered the drug according to the label.

B. Administrative Proceedings

In June 2009, SafeGuard issued to VRC a preliminary overpayment determination of approximately \$8.9 million, representing the amount charged for two-thirds of the doses administered by VRC against the label's instructions. In July of the same year, First Coast published an updated Local Coverage Determination under the title "Article Clarification" specifically aimed at eliminating payment for multi-dosing from single-use Lucentis vials. This publication stated that "when a single use vial is used and billed for three patients at 0.5 mg per patient . . . [t]he physician is then overstating his/her expense." In addition, First Coast adopted SafeGuard's overpayment determination and concluded that VRC "should have known [it was] not entitled to" the overpayment and was therefore liable to repay to Medicare \$8,982,706.98. VRC's request for reconsideration was denied and VRC complied with the repayment demand. VRC also pursued administrative review.

An administrative law judge ("ALJ") upheld the overpayment determination. The ALJ noted that VRC had not complied with the drug's label. As a result, the ALJ concluded, the injection of more than one dose from one vial of Lucentis was not "safe and effective" and was not covered by Medicare Part B. The Medicare

Appeals Council subsequently affirmed the ALJ's decision.³ The Appeals Council held that Lucentis injections are "medically reasonable and necessary [only] to the extent the drug [is] administered consistent with its FDA-approved label." In addition, the Appeals Council held that VRC "knew, or could reasonably be expected to know, that the Lucentis injections . . . would not be covered by Medicare," so it was liable for the overpayment under 42 U.S.C. § 1395pp(a).

C. District Court Proceedings

VRC filed suit in the Southern District of Florida. The district court granted summary judgment for HHS. It gave deference to the agency's decision because "[p]laintiff has failed to demonstrate that the Secretary[']s decision was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." VRC now appeals.

II.

We review *de novo* grants of summary judgment, and we the same legal standards that bound the district court. *Whatley v. CNA Ins. Cos.*, 189 F.3d 1310,

³ The Appeals Council's decision refined the ALJ's decision in one detail. The ALJ found that VRC's administration of Lucentis was not medically reasonable and necessary. On the other hand, the ALJ calculated the proper payment for all three doses of Lucentis, allowing VRC to charge for all three doses from a single vial, but at a reduced billing rate that reflected a two-thirds decrease in the allowed rate. The Appeals Council held that this was contradictory: If VRC's administration of Lucentis was not reasonable, it should not receive reimbursement for more than one dose per vial. The Appeals Council modified the decision accordingly and held that the administration of a single 0.5-mg dose of Lucentis from a single vial was reasonable and should be reimbursed at the full rate of \$2,025, while the administration of second and third doses from the same vial was not reasonable because it did not comply with the drug's label.

1313 (11th Cir. 1999). Summary judgment is appropriate when the record reflects show no genuine issue of material fact and demonstrates that the moving party is entitled to judgment as a matter of law. *Connelly v. Metro. Atlanta Rapid Transit Auth.*, 764 F.3d 1358, 1363 (11th Cir. 2014).

In a dispute related to Medicare reimbursement, “[t]he findings of the [Secretary] as to any fact, if supported by substantial evidence, shall be conclusive.” 42 U.S.C. §§ 405(g), 1395ff(b)(1)(A). We therefore limit our review to whether substantial evidence supports the Secretary’s findings and whether the Secretary applied the correct legal standards. *Wilson v. Barnhart*, 284 F.3d 1219, 1221 (11th Cir. 2002); *see* 42 U.S.C. § 1395ff(b)(1)(A) (incorporating into Medicare Act the standard of review set forth in 42 U.S.C. § 405(g)).” *Gulfcoast Med. Supply, Inc. v. Sec’y, Dep’t of Health & Human Servs.*, 468 F.3d 1347, 1350 n.3 (11th Cir. 2006). Substantial evidence “is ‘such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.’” *Barnes v. Sullivan*, 932 F.2d 1356, 1358 (11th Cir. 1991) (citations omitted). “We review de novo the district court’s decision on whether substantial evidence supports the ALJ’s decision.” *Wilson*, 284 F.3d at 1221.

As for legal conclusions, the Administrative Procedure Act limits our review to determining whether the agency’s actions were “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” 5 U.S.C. § 706. “[T]his

standard is exceedingly deferential.” *Fund for Animals, Inc. v. Rice*, 85 F.3d 535, 541 (11th Cir. 1996). As we have previously explained, “the arbitrary and capricious standard gives an appellate court the *least* latitude in finding grounds for reversal; ‘[a]dministrative decisions should be set aside in this context . . . only for substantial procedural or substantive reasons as mandated by statute, . . . not simply because the court is unhappy with the result reached.’” *Rice*, 85 F.3d at 541-42 (citations omitted). We are not permitted to substitute our judgment for that of the agency “concerning the wisdom or prudence of the proposed action.” *Id.* We have further recognized that our deference to the Secretary’s judgment is especially warranted in the context of Medicare “[b]ecause Medicare is a ‘complex and highly technical regulatory program.’” *Gulfcoast Med. Supply*, 468 F.3d at 1353 (citation omitted).

III.

“Title XVIII of the Social Security Act, 79 Stat. 291, as amended, 42 U.S.C. § 1395, *et seq.*, commonly known as the Medicare Act, establishes a federally subsidized health insurance program to be administered by the Secretary.” *Heckler v. Ringer*, 466 U.S. 602, 605, 104 S. Ct. 2013, 2016 (1984). Medicare Part B creates voluntary supplemental medical insurance covering, among other things, doctors’ services and outpatient care. 42 U.S.C. § 1395k(a)(2). Under the program, Medicare beneficiaries receive medical treatment, and providers submit

claims for government reimbursement. 42 U.S.C. § 1395n. To prevent abuse and to control costs, Congress has authorized Medicare reimbursement for “medical and other health services” if they are “reasonable and necessary” only. *See* 42 U.S.C. §§ 1395k(a)(1), 1395y(a)(1)(A). “Medical and other health services” include “services and supplies [] furnished as an incident to a physician’s professional service.” 42 U.S.C. § 1395x(s)(2)(A). Under the Medicare Act, the Secretary has the authority “to determine what claims are covered by the Act ‘in accordance with the regulations prescribed by him.’” *Ringer*, 466 U.S. at 605, 104 S. Ct. at 2016 (citing 42 U.S.C. § 1395ff(a)).

The Centers for Medicare and Medicaid Services (“CMS”) within HHS are responsible for the administration of Medicare Part B, including the determination of coverage for physician-administered drugs. *HHS, CMS Reorganization Order*, 66 Fed. Reg. 35437 (July 5, 2001). CMS published the Medicare Benefit Policy Manual to provide guidance on Medicare Part B coverage. This manual instructs that “[i]n order to meet all the general requirements for coverage under the ‘incident to’ provision . . . the cost of the drug or biological must represent an expense to the physician.” Pub. No. 100-02, Ch. 15, § 50.3. The Policy Manual further requires that drugs be “safe and effective.” *Id.* § 50.4.1. Drugs are “safe and effective” when “used for the indications specified on the labeling.” *Id.*

Regional Medicare contractors, in turn, are authorized to issue Local Coverage Determinations governing when items and services are “reasonable and necessary” and therefore payable by Medicare. 42 U.S.C. § 1395ff(f)(2)(B). CMS published the Medicare Program Integrity Manual to guide regional contractors in their local coverage determinations. Pub. No. 100-08, Ch. 13. This manual instructs that coverage determinations should be based on whether an item is “[a]ppropriate . . . in terms of whether it is [f]urnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient’s condition.” *Id.* § 13.5.1.

In the instant case, First Coast, the regional Medicare contractor for Florida, issued a Local Coverage Determination, acknowledging Medicare coverage for Lucentis. As described above, the Local Coverage Determination incorporated the label’s instruction: “Each vial should only be used for treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used.” Based on this instruction, the Secretary, through First Coast and SafeGuard, determined that Medicare would not reimburse for multiple doses of Lucentis administered from the same vial.

VRC argues that the Secretary’s determination was unlawful. First, VRC asserts that the Secretary exceeded her authority in calculating the reimbursement allowance for Lucentis at anything less than full payment for every 0.5-mg dose,

regardless of how many doses were administered per vial. Second, VRC contends that the Secretary's determination that administering more than one dose per vial was medically unreasonable and unnecessary was arbitrary and capricious and not supported by substantial evidence. Finally, VRC maintains that even if the Secretary's decision was proper, it should be applied prospectively only, and VRC should not be held liable to repay Medicare the overpayment amount of \$8.9 million. We do not find merit in VRC's arguments.

A. VRC's Charge to Medicare did not Reflect its Expense and was Not Medically Reasonable.

The Secretary denied payment to VRC on two grounds. Initially, the Secretary denied payment because VRC "overstated [its] expense" by billing Medicare for each 0.5-mg dose of Lucentis it administered, when it did not purchase and incur the expense of a full 2.0-mg vial for each dose. Later in the review process, the Secretary based her denial of payment on the finding that multiple doses were not medically reasonable and necessary.

Before addressing the merits, we consider a procedural argument urged by VRC. There is some indication that the two reasons offered by HHS were not offered contemporaneously. In the initial overpayment letter, HHS based its decision on "overstated expense."⁴ Only later in the review process—on review

⁴ In the initial overpayment letter from First Coast, HHS stated that "medical necessity is not an issue in this case" and that the only issue was the overstated expense. VRC attempts to

before the Medicare Appeals Council—did HHS assert that multi-dosing was medically unreasonable. VRC insinuates that this history automatically indicates arbitrariness. We disagree.

First, it is not clear that HHS ever surrendered its first reason. In the district court, the Secretary expressly relied on the overstated-expense theory. And on appeal, in its brief, HHS contests VRC’s assertion regarding the fiscal effects of the Secretary’s position, an argument closely related to the overstated-expense theory.⁵ But even if HHS had changed its reason for denying payment, that, in and of itself, would not necessarily make the Secretary’s decision arbitrary.

The Supreme Court has repeatedly held that an agency can change its position on an issue, so long as it gives a proper reason for doing so. *See, e.g., F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 129 S. Ct. 1800 (2009) (holding agency need not provide a more substantial reason for a change in policy than the arbitrary standard); *Nat’l Cable & Telecommunications Ass’n v. Brand X*

argue that this statement waived the Secretary’s subsequent position that multi-dosing was medically unreasonable. We disagree. Even without considering whether the Secretary can permissibly change her reasoning justifying a particular application of a rule in a given case, all that can be surmised from this single line in the letter is that the overpayment determination was not based on concerns that VRC was administering drugs to patients who did not need them. In other words, HHS was conceding that Lucentis is medically reasonable for the treatment of AMD in general. There is nothing in the letter indicating that HHS was condoning the practice of multi-dosing from single vials of Lucentis.

⁵ Below, we disagree with the Secretary’s argument on this point and recognize the truth of VRC’s position that the resolution of this case is fiscally neutral to Medicare. *See infra* Part I.A. However, the point here is that the Secretary did raise the overstated expense issue on appeal and it is appropriate for us to address in this opinion.

Internet Servs., 545 U.S. 967, 981, 125 S. Ct. 2688, 2699 (2005) (“Agency inconsistency is not a basis for declining to analyze the agency’s interpretation under the *Chevron* framework”); *see also Am. Petroleum Inst. v. E.P.A.*, 661 F.2d 340, 355 (5th Cir. 1981) (“Nothing in the Administrative Procedure Act prohibits an agency from changing its mind.”). Because it is not clear that the Secretary intended to forgo her initial argument, we address both reasons that the Secretary proffers.

1. *Overstated Expense*

VRC argues that the Secretary’s first rationale is flawed because Medicare reimbursement is not related to the physician’s expense. For support, VRC cites *Hays v. Sebelius*, 589 F.3d 1279 (D.C. Cir. 2009). That case concerned whether the Secretary could deny payment for DuoNeb, a drug used to treat Chronic Obstructive Pulmonary Disease. *Id.* at 1280. DuoNeb provides a combination of two separate drugs in one dose and is more expensive than purchasing the component drugs separately. *Id.* The Secretary argued that Medicare’s “least costly alternative policy” required that reimbursement be limited to the cost of the two separate drugs rather than the higher cost of DuoNeb. *Id.* The District of Columbia Circuit held that the statute is unambiguous in its instruction to the Secretary: “either an item or service is reasonable and necessary, in which case it may be covered at the statutory rate, or it is unreasonable or unnecessary, in which

case it may not be covered at all.” *Id.* at 1282. As the court explained, “Nothing in the statute authorizes the least costly alternative policy.” *Id.* at 1283.

We think *Hays* inapposite. *Hays* construed the Medicare statute to require Medicare to pay for any drug it deems reasonable and necessary, without regard to alternative methods that would save Medicare money. Here, the Secretary did not demand that VRC administer a cheaper alternative than Lucentis. Instead, the Secretary demanded only that VRC’s bill to Medicare reflect the expense incurred by VRC in purchasing the drug. Medicare’s policy is that “[t]he charge . . . for the drug or biological must be included in the physician’s bill, and the cost of the drug or biological *must represent an expense to the physician.*” Medicare Benefit Policy Manual, Pub. No. 100-02, Ch. 15, § 50.3 (emphasis added). Nothing in the statute forbids the Secretary from relating Medicare reimbursement to the physician’s expense. On the contrary, the very concept of “reimbursement” contemplates payment for money that was actually spent. *See Reimbursement, The Am. Heritage Dictionary* (4th ed. 2000) (“1. To repay (money spent); refund. 2. To pay back or compensate (another party) for money spent or losses incurred . . .”); *see also Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 205, 109 S. Ct. 468, 470 (1988) (“health care providers are *reimbursed* by the Government for *expenses incurred* in providing medical services to Medicare beneficiaries.”) (emphasis added).

VRC also points to a recent CMS publication that describes Medicare's policy for reimbursing medical providers. 81 Fed. Reg. 13229 (March 11, 2016). This publication explains that "Medicare pays for most drugs . . . at ASP+ 6 [Average Sales Price + six percent]. . . . The ASP payment amount does not vary based on the price an individual provider or supplier pays to acquire the drug." *Id.* at 13231; *see also id.* at 13253 ("Medicare pays this price regardless of the price a provider pays to acquire the drug."). VRC argues that this publication contradicts the Secretary's position.

Again, we disagree. Under CMS's policy, once it has determined the Average Sales Price and calculated the 106% reimbursement rate for a given drug, CMS does not inquire into individual medical providers' costs when calculating reimbursement. Instead, CMS reimburses at the 106% rate, regardless of the possibility that a given provider may have obtained the drug at a reduced rate. That is not what happened here. VRC's profits from treating AMD with Lucentis did not stem from the advantage of purchasing the drug at a reduced rate. VRC bought Lucentis at the market rate. Its extraordinary profits arose from using a single-dose-approved vial for three patients, in violation of the FDA-approved instructions.

VRC next suggests that Medicare's policy to pay for overfill runs counter to the position that HHS has taken with respect to VRC. Under the overfill policy,

CMS “reimburse[s] suppliers for the total number of units administered CMS does not make any payment determinations based on the absence or presence of ‘overfill’ in a vial.” “Overfill” is “[a]ny excess free product . . . provided without charge” when a physician purchases a vial of a drug, in excess of amounts “defined by the product packaging.” 75 Fed. Reg. 73170, 73466 (Nov. 29, 2010). VRC argues that if Medicare reimburses for overfill, even though overfill is obtained without cost, certainly Medicare should reimburse for the full contents of a vial of Lucentis in order to reimburse the full expense to the provider in purchasing the vial.

We are not persuaded. Medicare’s policy to reimburse for overfill means only that where a manufacturer does not charge for excess drug, Medicare will not recalculate its unit price for the excess drug. But this policy is inapplicable in a situation where Medicare has calculated the unit price for a drug based on the presumption that some of a vial’s content will necessarily not be used per the drug’s instructions. In such a case, if a physician does not comply with the instructions and multi-doses, the presumption for the calculation is lost and a recalculation is in order.

Here, Medicare determined the unit price for Lucentis, taking into account the full contents of a Lucentis vial and the label instructions for administration. Because only 0.5 mg of a 2.0-mg vial should actually be administered under the

FDA-approved labeling, the price of the full vial was assigned as the price of a single 0.5-mg dose. Therefore, every time a physician buys a single 2.0-mg vial and administers a single 0.5-mg dose from the vial (disposing of 1.5 mg of the drug), the physician is compensated for the full cost of purchasing the 2.0-mg vial, despite the fact that the doctor administers only 0.5 mg. Indeed, upon discovery of VRC's actions, First Coast issued an article clarification specifically recalculating the unit price of Lucentis if a physician used a single vial to administer more than one dose.

We also reject VRC's argument that the Secretary's decision was arbitrary because the total amount of reimbursement would not have changed whether Medicare reimbursed at the full amount of \$2,025 for three doses of a single vial or required that every dose be administered from separate vials. This argument fails to account for Medicare's lawful policy that reimbursement to providers should reflect more-or-less actual expense to the physician. *See Bowen*, 488 U.S. at 205, 109 S. Ct. at 470. And since that policy is not arbitrary or capricious, Medicare's decision to reimburse VRC for only its actual expenditure on Lucentis cannot be arbitrary or capricious, either.

2. Medical Reasonableness and Necessity

As an alternative basis for denying reimbursement, the Secretary reasoned that multiple doses of Lucentis from a single vial were medically unreasonable,

based on the FDA-approved labeling instructions allowing for only a single dose from a single vial. VRC contends that this decision was arbitrary.

a. Medical Distinction between Doses

First, VRC argues that it is arbitrary for the Secretary to treat the first dose of Lucentis from a given vial as medically reasonable and the other two doses from the same vial as medically unreasonable. We disagree. The inquiry into whether a drug is medically reasonable and necessary in the Medicare reimbursement context is not limited to an assessment of whether the drug is suited to treat the disease or condition for which it was administered. The inquiry also accounts for whether a drug was administered properly. *See Medicare Policy Integrity Manual, Pub. No. 100-08, Ch. 13, § 13.5.1.* Because administering more than one dose of Lucentis from one vial violated the drug's FDA-approved labeling, the Secretary reasonably could have concluded that multi-dosing was medically inappropriate.

b. Local Coverage Determination

Next, VRC argues that its administration of multi-doses of Lucentis complied with the then-existing conditions for Medicare coverage. First Coast's 2008 Local Coverage Determination stated that "Medicare will consider [Lucentis] medically reasonable and necessary for patients" with AMD. VRC asserts that nothing in this initial Coverage Determination described the proper process for preparation of injections or prohibited multi-dosing. In support, VRC points to the

fact that in 2009 First Coast published an “Article Clarification” specifically reducing payment for multi-dosing, the implication being that until then multi-dosing was acceptable and would be reimbursed at the full rate.

We disagree. The 2008 Coverage Determination expressly incorporated the drug’s labeling: “Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used.” We cannot say that it was arbitrary or capricious for HHS to read this instruction as a prohibition against administering more than one dose from a single vial, regardless of whether VRC proposes another reasonable interpretation of the labeling. Nor does the Secretary’s issuance of the 2009 “Article Clarification” undermine the reasonableness of her original interpretation of the labeling. Rather, the Article Clarification is entirely consistent with the Secretary’s original interpretation. We review the Secretary’s decision for arbitrariness, and reading the instruction as prohibiting multi-dosing is not arbitrary.

c. Practice of Multi-Dosing

VRC also contends that CMS encourages the practice of multi-dosing from single-use vials and that the practice is widely accepted in the medical community. In support of this position, VRC invokes the Medicare Claims Processing Manual, which states that “CMS encourages physicians, hospitals and other providers to schedule patients in such a way that they can use drugs or biologicals most

efficiently, in a clinically appropriate manner.” Pub. No. 100-04, Ch. 17, § 40 [A162.]. In addition, VRC relies on a response to a “Frequently Asked Question” (“FAQ”) that CMS published on its website in March 2011. The question asked whether Medicare would provide coverage “for a drug from a single dose vial if it is administered to more than one beneficiary[.]” CMS responded that it “encourages physicians . . . to care for and administer to patients in such a way that they can use drugs or biologicals most efficiently, in a clinically appropriate manner. . . . [O]ur policies neither encourage or [sic] prohibit the administration of more than one dose from a single dose vial to one or more beneficiaries.”⁶ Finally, VRC points to the Secretary’s policy to reimburse physicians for multiple doses from single vials of Botox and Avastin. VRC contends that both of these drugs come in “single-use” vials, yet Medicare reimburses for multiple doses.

These arguments lack merit. Both publications on which VRC relies include the important disclaimer that multiple doses are acceptable only if administered “in a clinically appropriate manner.” And the CMS response to the FAQ explains that “clinically appropriate methods” are determined by “numerous factors, including but not limited to: approved labeling.”

⁶ VRC also cites FDA publications permitting repackaging and multi-dosing from single-use vials, arguing that even if it was required to follow the drug’s label’s instructions, the FDA itself disregards them. The relevant publications address repackaging in specialized, licensed facilities with a high level of air quality to avoid contamination. *See Draft Guidance Mixing, Diluting, Or Repackaging Biological Products Outside The Scope Of An Approved Biologics License Application Guidance For Industry*, 2015 WL 1735391. They are inapplicable to VRC, which is not a licensed repackaging facility.

VRC's analogy to Botox and Avastin is misplaced as well. Botox is a vacuum-dried powder that is available in 100-unit vials only. Before administration, the physician must reconstitute all of the powder from the single vial with saline solution. Once reconstituted, the drug must be stored in a refrigerator and used within 24 hours. To prevent physicians from saving the drug for use beyond 24 hours, Botox is labeled "Single Patient Use." But the Botox packaging insert instructs, "A new, sterile, needle and syringe should be used to enter the vial on each occasion for removal of Botox." So the drug's instructions expressly contemplate multiple doses from a single vial. That, of course, is not the case with Lucentis.

As for Avastin, it is sold in 100- or 400-mg vials, must be diluted before administration, and should be stored for no more than eight hours. Avastin is FDA-approved only for the treatment of certain forms of cancer; treatment of AMD is an off-label use. Therefore, although the Avastin instructions state that the physician should "[w]ithdraw [the] necessary amount . . . [and] [d]iscard any unused portion," these instructions apply only where the drug is used for the treatment of cancer, in which case a single dose varies between 100 mg and 400 mg. But Medicare has a separate procedure for determining coverage for off-label use, taking into account accepted standards of medical practice for that drug's off-label use, which often vary from accepted standards for on-label use. *See*

Medicare Benefit Policy Manual, Pub. No. 100-02, Ch. 15, § 50.2. When Avastin is used for the treatment of AMD, a single dose is as small as 1.25 mg. The accepted medical practice is to use multiple doses from a single vial of Avastin when it is being used to treat AMD. In this context, as with Botox, Avastin's admonition of "single use" is intended to prevent physicians from using product that has been stored past the acceptable eight-hour timeframe.

Unlike Avastin, Lucentis's on-label, FDA-approved use is for treating AMD. Its label expressly states that each vial should be used for only the treatment of a single eye and the excess drug should be drawn into the syringe and expelled. VRC administered Lucentis for its on-label use and failed to follow the instructions regarding that use, without any support from an established medical practice that differs from the label's instructions.⁷

In light of these distinctions between Lucentis and the other drugs VRC identifies, we cannot conclude that the Secretary's policy to treat Lucentis differently is arbitrary or capricious.

B. The Secretary's Decision was Supported by Substantial Evidence.

VRC argues that the Secretary's decision violated the Administrative Procedure Act because it was not based on substantial evidence. Above we have

⁷ VRC attempts to analogize Lucentis to Kenalog as well. This analogy also fails because, unlike Lucentis, Kenalog does not include an instruction to withdraw the entire contents and expel the excess.

already discussed much of the basis for VRC's argument. In addition, VRC raises some additional points.

First, VRC argues that the Secretary placed undue reliance on Lucentis's labeling because the Local Coverage Determination is the definitive determination by a Medicare contractor "respecting whether or not a particular item or service is covered." 42 U.S.C. § 1395ff(f)(2)(B). Since First Coast's initial Local Coverage Determination did not incorporate the instruction to discard unused Lucentis as a condition for payment, VRC contends it was not bound to follow the FDA-approved instructions to receive reimbursement.

But even assuming that the Local Coverage Determination is the definitive one, the Local Coverage Determination at issue included the instruction that each vial be used for a single eye only. This instruction necessarily implies that excess drug above the 0.5-mg dose should be discarded. In addition, the Local Coverage Determination need not include all instructions regarding the administration of the drug. The purpose of the Local Coverage Determination is to instruct physicians under what terms they will receive reimbursement. To that end, First Coast described the basic method of administering the drug, describing the amount of a single dose and requiring a new vial for each eye. The additional instructions on the label were not necessary for the description of the terms for reimbursement and

do not absolve VRC of its disregard of the instruction to discard remaining amounts.

In addition to Lucentis's label, the *Physician's Desk Reference* includes the instruction to discard unused product. Courts have recognized the *Physician's Desk Reference* as evidence of the medical standard for a given drug. *See Haught v. Maceluch*, 681 F.2d 291, 303 (5th Cir. 1982) (relying on *Physician's Desk Reference* to establish standard of care in a medical malpractice suit). While the *Physician's Desk Reference* is not conclusive evidence of the standard or accepted practice, the drug's label instructed that the excess drug should be discarded, the *Physician's Desk Reference* repeated the instruction, and VRC presented no evidence of a contrary accepted medical practice.⁸

C. VRC is Liable for the Overpayment.

Having determined that the Secretary's legal interpretation withstands judicial scrutiny and was supported by substantial evidence, we next consider VRC's argument that it is not liable for the overpayment because it acted in good faith when it accepted the payment. In support, VRC cites two sections of the

⁸ VRC raises additional points regarding a letter sent from Lucentis's manufacturer and the Centers for Disease Control and Prevention standards for repackaging that were relied on by the district court as a basis for affirming the Secretary's decision. We need not reach these points because sufficient grounds exist to affirm the Secretary's decision based on the drug's label and the *Physician's Desk Reference*.

Medicare Act: 42 U.S.C. § 1395pp and 1395gg. Neither of these sections relieves VRC of liability.

a. 42 U.S.C. § 1395pp

Under 42 U.S.C. § 1395pp(a), Medicare must reimburse a provider if the provider “did not know, and could not reasonably have been expected to know, that payment would not be made for such items or services.” VRC argues that it could not have reasonably been expected to know at the time that it administered the doses that the Secretary would not reimburse multi-doses of Lucentis.

In support of its argument, VRC once again relies on CMS’s policy to encourage multi-dosing. But CMS does not maintain a general policy to encourage physicians to contravene FDA-approved instructions without evidence to support such a practice. And for the reasons we have previously discussed, VRC could have and should have reasonably known when it administered the doses that it would not be “reimbursed” three times for a single vial.

For the same reasons, we reject VRC’s argument that the Secretary retroactively created policy through the HHS Medicare Appeals Council. Through the initial 2008 Local Coverage Determination issued by First Coast, Medical providers received sufficient notice that multi-dosing would not be covered at the rate of \$405 per unit. In short, on this record, VRC could and should have

reasonably known when it administered the multiple doses that it would be reimbursed for only the number of vials it actually paid for.

b. 42 U.S.C. § 1395gg

Section 1395gg of the Medicare Act provides that the Secretary may waive recoupment where the provider was “without fault” when it received overpayment. 42 U.S.C. § 1395gg. The CMS Financial Management Manual instructs that a party is “without fault” when it “exercised reasonable care in billing for, and accepting the payment.” Pub. No. 100-06, Ch. 3, § 90. “Reasonable care,” in turn, requires that the provider “made full disclosure of all material facts” and that, “[o]n the basis of information available to it, . . . [the provider] had reasonable basis for assuming that the payment was correct, or, if it had reason to question payment; it promptly brought the question to [Medicare’s] attention.” *Id.* VRC argues that HHS should waive its right to recoupment because VRC was without fault when it accepted the payment, and it dealt transparently with Medicare during the audit and review process.

We do not agree. VRC did not have a reasonable basis for assuming the payment was correct because its practice of multi-dosing was contrary to the drug’s instructions and was not based on established medical practice. At best, VRC “had reason to question payment,” in which case it should have brought the question to the attention of First Coast to resolve the issue. VRC dealt

transparently with First Coast and SafeGuard *after* receiving notice of overpayment. Transparency at this stage did not meet the standard of airing the question to the proper authorities before burdening them with an extensive review of VRC's records. We therefore agree with the Medicare Appeals Council that VRC was not "without fault" when it accepted the overpayment, and the Secretary was under no obligation to waive the right to recoupment.

IV.

For the foregoing reasons, we affirm the judgment of the District Court.

AFFIRMED.