United States Court of Appeals
For the First Circuit

Nos. 18-1146, 18-1147

IN RE: CELEXA AND LEXAPRO MARKETING AND SALES PRACTICES LITIGATION

PAINTERS AND ALLIED TRADES DISTRICT COUNCIL 82 HEALTH CARE FUND; DELANA S. KIOSSOVSKI; RENEE RAMIREZ, on behalf of herself and all others similarly situated; MARLENE T. LOCONTE,

Plaintiffs, Appellants,

MARTHA PALUMBO, individually and on behalf of all other persons similarly situated; PETER PALUMBO, individually and on behalf of all other persons similarly situated; JAYNE EHRLICH, individually and on behalf of all other persons similarly situated; ANNA MURRET, individually and on behalf of all other persons similarly situated; UNIVERSAL CARE, INC.; ANGELA JAECKEL; MELVIN M. FULLMER, on behalf of himself and all others similarly situated; NEW MEXICO UFCW UNION'S AND EMPLOYER'S HEALTH AND WELFARE TRUST FUND, on behalf of itself and all others similarly situated; ALLIED SERVICES DIVISION WELFARE FUND, on behalf of itself and all others similarly situated; TARA JOHNDROW, individually and on behalf of all others similarly situated; BRIAN ANSON, individually and on behalf of all others similarly situated; SCOTT A. WILCOX, on behalf of himself and all others similarly situated; MUNICIPAL REINSURANCE HEALTH INSURANCE FUND; RANDY MARCUS; BONNIE MARCUS; RUTH DUNHAM; TANYA SHIPPY; JILL POWELL,

Plaintiffs,

v.

FOREST PHARMACEUTICALS, INC.; FOREST LABORATORIES, INC.; FOREST LABORATORIES, LLC, successor in interest to Forest Laboratories, Inc.,

Defendants, Appellees,

PFIZER, INC.; WARNER LAMBERT COMPANY,

Defendants.

APPEALS FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

[Hon. Nathaniel M. Gorton, U.S. District Judge]

Before

Howard, Chief Judge,
Torruella and Kayatta, Circuit Judges.

R. Brent Wisner, with whom Michael L. Baum, Baum, Hedlund, Aristei & Goldman, P.C., Christopher L. Coffin, and Pendley, Baudin & Coffin, LLP were on brief, for appellants.

Andrew J. Ceresney, with whom Edwin G. Shallert, Kristin D. Kiehn, J. Robert Abraham, Debevoise & Plimpton LLP, John G. O'Neill, and Sugarman, Rogers, Barshak & Cohen, P.C. were on brief, for appellees.

January 30, 2019

KAYATTA, **Circuit Judge**. These consolidated appeals arise out of two so-called "off-label" prescription-drug-marketing cases aggregated for pretrial proceedings in the District of Massachusetts by order of the multidistrict litigation panel. Plaintiffs claim that the defendants, Forest Pharmaceuticals, Inc. and Forest Laboratories, Inc. (collectively "Forest"), engaged in fraud to push their antidepressant drugs on unsuspecting minors for whom the FDA had not approved the use of these medications. As we will explain, we reverse the dismissal of the claims brought by two of the four plaintiffs, and we vacate the denial of plaintiffs' motion to compel the production of additional documents by Forest. We otherwise affirm the challenged district-court rulings, including the denial of class certification.

I.

We begin by summarizing the relevant statutory and regulatory framework and by reciting the facts relevant to the plaintiffs' summary-judgment appeal in the light most favorable to the plaintiffs. See Boudreau v. Lussier, 901 F.3d 65, 71 (1st Cir. 2018).

A.

The Federal Food, Drug, and Cosmetic Act ("FDCA") requires drug manufacturers to obtain approval from the U.S. Food and Drug Administration ("FDA") before marketing a drug for a particular medical use. 21 U.S.C. § 355(a); see also Mut. Pharm.

Co., Inc. v. Bartlett, 570 U.S. 472, 476 (2013). To secure that approval, the drug manufacturer must submit to the FDA either a new-drug application ("NDA") or a supplemental new-drug application ("sNDA"), and the manufacturer must demonstrate the drug's efficacy for the indicated use in at least two double-blind, randomized-controlled trials ("DBRCTs"). See In re Neurontin Mktg. & Sales Practices Litig. (Kaiser), No. 04-cv-10739-PBS, 2011 WL 3852254, at *5 (D. Mass. Aug. 31, 2011), aff'd, 712 F.3d 21 (1st. Cir. 2013); see generally 21 C.F.R. § 314.105. The FDCA creates both civil and criminal penalties for drug manufacturers that promote the use of approved drugs for unapproved uses (referred to here as "off-label" uses). See 21 U.S.C. §§ 331(d), 333(a), 355(a); Lawton ex rel. United States v. Takeda Pharm. Co., 842 F.3d 125, 128 n.4 (1st Cir. 2016). The FDCA, however, does not prohibit doctors from prescribing drugs for off-label uses. Lawton ex rel. United States, 842 F.3d at 128 n.4.

B.

Forest manufactures and markets prescription drugs, including the antidepressant medications Celexa and Lexapro. Celexa and Lexapro are chemically similar selective serotonin reuptake inhibitors ("SSRIs"), a class of antidepressants that affect a patient's mood by blocking the reabsorption of the neurotransmitter serotonin in the brain, Eli Lilly & Co. v. Teva Pharm. USA, Inc., No. 05-1044, 2005 WL 1635262, at *1 (Fed. Cir.

July 13, 2005). The FDA approved Celexa and Lexapro for the treatment of major depressive disorder ("MDD") in adults (i.e., individuals aged eighteen or over) in 1998 and 2002, respectively. Drug manufacturers, including Forest, had difficulty demonstrating that SSRIs were also effective in treating depression in children and adolescents. As of 2005, only Fluoxetine -- commercially known as Prozac -- had gained FDA approval for the treatment of pediatric depression. In 2009, the FDA approved Lexapro for the treatment of depression in adolescents (i.e., individuals of ages twelve through seventeen). The FDA has never approved Celexa for any pediatric use nor has it approved Lexapro as a treatment for depression in children (i.e., individuals under the age of twelve).

The record in this case nevertheless strongly suggests that Forest engaged in a comprehensive off-label marketing scheme from 1998 through 2009 aimed at fraudulently inducing doctors to write pediatric prescriptions of Celexa and Lexapro when Forest had insufficient reason to think that these drugs were effective for the treatment of depression in children and adolescents. Plaintiffs have pointed to substantial evidence that Forest sought to achieve this illicit aim by: (1) promoting Celexa's efficacy for the treatment of pediatric depression at medical conferences, at continuing-medical-education programs, and in press releases; (2) concealing negative clinical studies concerning Celexa's efficacy and safety; and (3) directly encouraging physicians to

prescribe Celexa and Lexapro for the treatment of pediatric depression.

For years, Forest nevertheless denied that it was engaged in the off-label promotion of these drugs. Forest Laboratories' Executive Vice President, Dr. Lawrence Olanoff, testified before Congress in 2004 that "because the FDA has not approved pediatric labeling for our products, Forest has always been scrupulous about not promoting the pediatric use of our antidepressant drugs, Celexa and Lexapro. That is the law, and we follow it." Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight & Investigations of the Comm. on Energy & Commerce, 108th Cong. 82 (2004) (statement of Dr. Lawrence Olanoff).

Even before Dr. Olanoff assured Congress of Forest's scrupulousness, a whistleblower had commenced a qui tam action, alleging that Forest had violated the False Claims Act ("FCA"), 31 U.S.C. § 3729(a), by fraudulently marketing and promoting Celexa and Lexapro for the off-label treatment of depression in pediatric patients. Complaint, Gobble v. Forest Labs., Inc., No. 03-10395-NMG (D. Mass. Mar. 4, 2003), ECF No. 1. The United States later intervened in that suit, and, in February 2009, the district court unsealed the United States' complaint. Order Granting Motion to Unseal, United States ex rel. Gobble, No. 03-10395-NMG (D. Mass. Feb. 24, 2009), ECF No. 64. The evidence belying Dr. Olanoff's

assurances to Congress turned out to be quite substantial. Ultimately, in September 2010, Forest paid a $39 million fine in connection with pleading guilty to criminal violations of the FDCA for its off-label promotion of Celexa between 1998 and 2002 and an additional $149 million to the United States to settle civil claims that Forest illegally promoted Celexa and Lexapro for pediatric use in 2002 through 2005.

C.

Within the following four years, over a dozen consumers and entities who paid for prescription drugs filed the lawsuits that led to this appeal. Initially, four plaintiffs joined in the notice of appeal. Only two, Renee Ramirez and the Painters and Allied Trades District Council 82 Health Care Fund ("Painters") have presented any argument on appeal. We refer to these two collectively as "plaintiffs."[1] Ramirez purchased Celexa and Lexapro for her young son from February 2003 through March 2010 on the recommendation of her son's neurologist. Painters has reimbursed its pediatric insureds for off-label prescriptions of Celexa and Lexapro since early 1999. Plaintiffs together seek

[1] Marlene LoConte and Delena Kiossovski joined in the notice of appeal but subsequently filed no brief, and the single brief filed by the other parties contains no argument at all for questioning the grounds upon which the district court dismissed the claims of LoConte and Kiossovski. We therefore deem their appeal of the judgments against them to be waived. See Vázquez-Rivera v. Figueroa, 759 F.3d 44, 46-47 (1st Cir. 2014).

recovery under the Racketeer Influenced and Corrupt Organizations Act ("RICO"), 18 U.S.C. § 1962(c)–(d), the Minnesota Consumer Fraud Act, Minn. Stat. § 325F.69, and the Minnesota Unfair Trade Practices Act, Minn. Stat. § 325D.13, and for unjust enrichment.

In June 2016, the district court denied Painters' motion to certify two nationwide classes of similarly situated health-insurance companies and health plans that had paid for or reimbursed off-label pediatric prescriptions of Celexa or Lexapro. In re Celexa & Lexapro Mktg. & Sales Practices Litig. (Painters I), 315 F.R.D. 116, 131 (D. Mass. 2016).[2] In rejecting class certification, the court reasoned that while Painters had satisfied the Rule 23(a) numerosity, commonality, typicality, and adequacy requirements, Painters had failed to establish that common questions of fact or law predominated over individual issues as required by Rule 23(b)(3). Id. at 123–31.

Subsequently, in March 2017, a dispute arose as a result of Forest's apparently belated production of two internal memoranda in advance of a deposition conducted by agreement after discovery had otherwise closed. The two documents contained

[2] Painters' motion for class certification provided no time period for the proposed Celexa class. At oral argument, however, plaintiffs' counsel clarified that plaintiffs only seek to challenge manufacturer-induced prescriptions for off-label uses made prior to the FDA's approval of Lexapro for adolescent use in March 2009. Thus, we construe Painters' appeal in accordance with this statement.

details regarding a study of Celexa's effectiveness. Forest revealed that it had not sought any responsive documents from its Clinical Supply Group in responding to Painters' discovery requests. The district court nevertheless denied Painters' motion to compel Forest's supplemental production of documents from this group, concluding that any such production would be cumulative. In re Celexa & Lexapro Mktg. & Sales Practices Litig. (Painters II), 288 F. Supp. 3d 483, 486–87 (D. Mass. 2018).

In due course, after deeming discovery complete and ruling on various interim motions, the district court entered summary judgment for Forest on plaintiffs' RICO claims, holding that neither Painters nor Ramirez could demonstrate injury. In re Celexa & Lexapro Mktg. & Sales Practices Litig. (Painters III), 289 F. Supp. 3d 247, 253–56 (D. Mass. 2018). The court then proceeded to dismiss plaintiffs' state-based allegations as deriving from their noncognizable RICO claims. Id. at 258–59. This appeal by Painters and Ramirez followed.

II.

Summary judgment is appropriate "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). In granting summary judgment dismissing all of plaintiffs' claims, the district court concluded that plaintiffs had no competent proof that either Celexa or Lexapro was

ineffective for treating depression in children or adolescents. We review this conclusion de novo. Martinez v. Petrenko, 792 F.3d 173, 179 (1st Cir. 2015).

A.

Prevailing on a RICO claim requires proof of an economic injury. See 18 U.S.C. § 1964(c) ("Any person injured in his business or property by reason of a violation of section 1962 of this chapter may sue therefor."). Plaintiffs allege injury in the form of payments made for ineffective drugs.[3] The district court therefore turned its attention to determining whether plaintiffs had enough evidence to allow a jury to find Celexa and/or Lexapro ineffective for treating pediatric depression. See Painters III, 289 F. Supp. 3d at 253–56. Four clinical trials and the FDA's 2009 approval of Lexapro for adolescents informed the district court's decision.

Starting in 1997, Lundbeck -- the developer of Celexa -- began conducting Study 94404, which focused on Celexa's efficacy in treating depression in adolescents. The study produced across-the-board negative results. Forest then conducted Study MD-18 in an attempt to demonstrate Celexa's effectiveness in both children

[3] In its opposition to Forest's motion for summary judgment, Painters argued that it need not demonstrate that Celexa and Lexapro are ineffective in treating pediatric depression to establish RICO injury. The district court rejected this argument in its order granting Forest's motion, and Painters has not developed any challenge to that ruling on this appeal.

and adolescents. The efficacy results of MD-18 are difficult to assess because Forest bungled the study: Some participants randomized into the active treatment group were dispensed nongeneric, pink tablets in one portion of the trial, potentially unblinding both the individuals who received these pills and the researchers conducting the study. The MD-18 study only demonstrated statistically positive results when these potentially unblinded participants were included. Finally, in 2002–2004 and 2005-2007, Forest conducted two additional clinical trials. Study MD-15 examined Lexapro's efficacy in children and adolescents and achieved negative results. Study MD-32 set out to test Lexapro's effectiveness in treating only adolescents and achieved statistically significant positive results.

Based upon the results of MD-32 and the Celexa MD-18 study, Forest submitted an sNDA to the FDA in 2008. In 2009, the FDA approved the application, allowing Forest to market Lexapro for use in adolescents. Forest did not seek such approval for Celexa.

Plaintiffs' evidence that Celexa and Lexapro were ineffective for the pertinent indications consisted of the following: The FDA has neither approved Celexa for treating depression in children or adolescents nor has it approved Lexapro for use in children; Study 94404 demonstrated only a detrimental effect of Celexa in treating depression in adolescents; Study MD-

18 was corrupted and showed no beneficial effect in children and adolescents unless the potentially unblinded participants are included in the results; and Study MD-15 produced uniformly negative results in testing Lexapro's efficacy in children and adolescents. In addition, plaintiffs produced expert testimony opining that the positive results in MD-32 were not of clinical significance and that MD-18 should properly be considered a negative trial. Plaintiffs also provided the results of a 2016 meta-analysis study that found that neither Celexa nor Lexapro had any more beneficial effect than a placebo in treating pediatric depression.

There is also evidence in the record before us, however, that cuts the other way. In September 2002, the FDA accepted Study MD-18 as a positive trial that would support a determination of Celexa's effectiveness for the treatment of MDD in adolescent patients. And in January 2003, the FDA also stated that MD-18 could be employed to support an application for FDA approval "for both Celexa and Lexapro, in pediatric patients with [MDD]." The FDA relied in part on these findings in approving Lexapro for the treatment of depression in adolescents in March 2009. Further, Forest points out that neither Painters nor Prime Therapeutics ("Prime"), Painters' pharmacy-benefits manager, has taken any effort to limit or remove from its formulary pediatric prescriptions of Celexa and Lexapro.

This record raises two questions. First, do the FDA's various pronouncements or actions close the door on any effort to convince a jury that either Celexa or Lexapro was ineffective? Second, to the extent that the FDA's pronouncements and actions are not preclusive, is the evidence in this case nevertheless insufficient to support a jury finding of ineffectiveness?

1.

Forest claims that two of our recent decisions -- D'Agostino v. ev3, Inc., 845 F.3d 1 (1st Cir. 2016), and In re Celexa & Lexapro Mktg. & Sales Practices Litig. (Marcus), 779 F.3d 34 (1st Cir. 2015) -- answer the first question in the affirmative by deeming FDA approval dispositive. Even were we to find it convincing, this argument would not cover all the challenged uses at issue in this appeal. The FDA has never approved Celexa for any of the off-label uses for which Forest promoted it. Nor has it approved Lexapro for the treatment of MDD in children under the age of twelve. So Forest's reliance on actual FDA approval to foreclose a jury determination of inefficacy must be limited to Forest's marketing of Lexapro for adolescent use and, perhaps as well, to the question of how to construe MD-18.

In any event, even as thus limited, we do not find Forest's reliance on D'Agostino convincing. The claim in D'Agostino concerned the sale of medical devices after the FDA had approved the devices for the uses for which they were sold.

D'Agostino, 845 F.3d at 3, 7–9. In rejecting a challenge to those post-approval sales under the False Claims Act based on alleged pre-approval fraud on the FDA, we reasoned that "[t]o rule otherwise would be to turn the FCA into a tool with which a jury of six people could retroactively eliminate the value of FDA approval and effectively require that a product largely be withdrawn from the market even when the FDA itself sees no reason to do so." Id. at 8. Here, by contrast, plaintiffs challenge only the promotion of Celexa and Lexapro for uses that were off-label (i.e., not FDA-approved) at the time Forest promoted and sold the drugs.[4] When Forest is said to have made those marketing efforts, it could not have pleaded reliance on FDA approval. If a jury were to hold Forest liable for such pre-approval marketing, it would simply be telling Forest that it should not have marketed that which Congress under the FDCA does not want it to market: drugs for unapproved uses. We therefore see no reason to accord to Forest the preclusive protection for pre-approval promotion that FDA approval provided the medical-device manufacturer for post-approval conduct in D'Agostino.[5]

[4] Though plaintiffs' complaints do not explicitly limit their RICO and state-law claims to the period prior to FDA's March 2009 approval of Lexapro, plaintiffs' counsel indicated at oral argument that plaintiffs do not challenge Forest's post-approval marketing of Celexa and Lexapro.

[5] For similar reasons, Forest's reliance on Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 348 (2001), in which the Supreme Court rejected as preempted state fraud-on-the-FDA claims,

Nor does our opinion in Marcus aid Forest in this case. In Marcus, we rejected a challenge to a drug label based on information that was "plainly known to the FDA prior to approving the label." 779 F.3d at 43. We made clear in doing so, however, that we were merely applying the state-law preemption principles the U.S. Supreme Court laid out in PLIVA, Inc. v. Mensing, 564 U.S. 604 (2011), and Wyeth v. Levine, 555 U.S. 555 (2009). See Marcus, 779 F.3d at 40–43 (explaining that a drug manufacturer can only be held liable under state law for inadequate warning in an FDA-approved label when the drug manufacturer can, "of its own volition, . . . strengthen its label in compliance with its state tort duty" (quoting PLIVA, Inc., 564 U.S. at 624)). Marcus, accordingly, is inapposite.

This is not to say that the FDA's 2009 approval of Forest's sNDA for Lexapro is irrelevant to this case. Certainly the approval and the FDA's reliance on MD-18 provide what many jurors may view as strong evidence confirming that Lexapro, and perhaps Celexa as well, have always been efficacious in treating pediatric depression. The common law has long recognized that agency approval of this type is relevant in tort suits. See Restatement (Third) of Torts: Prod. Liab. § 4 (Am. Law Inst. 1998)

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and its progeny is misplaced. Plaintiffs question the efficacy of Celexa and Lexapro only for off-label uses; their claims, accordingly, are not predicated on a fraud-on-the-FDA theory of liability.

("[C]ompliance with an applicable product safety statute . . . is properly considered in [a product defect case]."). But the common law also recognizes that such evidence is not always preclusive. Id. ("[S]uch compliance does not preclude as a matter of law a finding of product defect."). And while there are strong reasons for treating such evidence as preclusive when the challenged sales are made in reliance on agency approval, those same reasons cut the other way when the sales are made without approval, and certainly when made unlawfully, as we must assume they were here.

2.

Having decided that the FDA's subsequent approval of Lexapro does not preclude proving that pre-approval uses of these drugs were ineffective, we turn to addressing whether plaintiffs may proceed with a claim based on product ineffectiveness when the evidence of efficacy is conflicting. This is more or less the question we left unanswered in Kaiser. See Kaiser, 712 F.3d at 49 (declining to address what evidentiary standard would be needed to demonstrate efficacy "if the results of DBRCTs were equivocal" or "if there were a different mix of DBRCT and non-DBRCT evidence").[6]

[6] To advance its preferred interpretation of the term "equivocal" in Kaiser, each party dedicates a significant portion of its brief to sparring over whether the DBRCT evidence in the Neurontin cases was, in fact, mixed. We need not address this question because, as we explain, Painters' RICO claim survives summary judgment even though the evidence of inefficacy is mixed. We note, however, that the DBRCTs in the Neurontin case were not uniformly negative as Forest would have us believe. Rather, the

Generally speaking, "conflicting evidence" is the hallmark of an issue that calls for factfinding, not summary judgment. See, e.g., Adria Int'l Grp. v. Ferre Dev., Inc., 241 F.3d 103, 111 (1st Cir. 2001) (finding summary judgment inappropriate when evidence presented was "contested and contradictory"); see also 10A Charles Alan Wright et al., Federal Practice and Procedure § 2712 (4th ed. 2018) ("[S]ummary judgment is not a substitute for the trial of disputed fact issues."). We see no reason to deviate from that general rule merely because the product marketed illegally is one that was later approved for lawful sales.[7] In short, why should we forgo customary fact-finding by the jury so as to reward unlawful conduct aimed at getting children to consume unapproved drugs?

Forest also argues that plaintiffs' evidence of ineffectiveness falls short of proving injury because Painters has not produced "individualized" proof that Celexa or Lexapro was ineffective for any particular insured. By "individualized" proof, Forest appears to mean testimony from a patient (or from a

district court noted both positive and negative clinical studies in reviewing the parties' evidence of Neurontin's efficacy for the at-issue off-label conditions. See Kaiser, 2011 WL 3852254, at *34–46 (reviewing mixed DBRCT results).

[7] Nor is summary judgment for Forest warranted due to the fact that Painters has not directed the removal of Celexa and Lexapro for pediatric uses from its drug formulary. As we held in Kaiser, it is "within the factfinder's province to weigh this evidence." Kaiser, 712 F.3d at 41.

doctor concerning that patient) that the patient experienced no beneficial effects from the drug. While evidence of that type could be probative, certainly it is not the only way to prove that a drug is ineffective. Indeed, given that (1) an ineffective drug may trigger a placebo effect in a given individual and (2) an effective drug may not benefit all users, individualized proof might well be less probative than the type of expert, study-based testimony that plaintiffs have offered. In any event, as we already held, such individualized proof is certainly not required. See In re Neurontin Mtkg. & Sales Practices Litig. (Harden), 712 F.3d 60, 69 (1st Cir. 2013) ("[W]e reject Pfizer's position that these plaintiffs must prove the individual, subjective ineffectiveness of each off-label prescription in order to establish injury. . . . The Harden plaintiffs have proffered clinical trial evidence that Neurontin is ineffective . . ., which is certainly enough to raise a genuine issue of fact on the effectiveness issue." (citation omitted)); In re Neurontin Mtkg. & Sales Practices Litig. (Aetna), 712 F.3d 51, 59–60 (1st Cir. 2013).

In sum, we hold that the FDA's 2009 approval of Lexapro does not preclude a jury from concluding that the off-label uses of Celexa and Lexapro at issue in this case were ineffective in treating pediatric depression. Moreover, plaintiffs have provided competent and sufficient evidence -- through DBRCTs, expert

testimony, and peer-reviewed literature -- to raise a genuine issue of material fact as to the efficacy of these drugs for pediatric use. Accordingly, the district court erred in granting summary judgment for Forest on plaintiffs' RICO and state-law claims on this basis.

B.

In addition to demonstrating economic injury, a RICO plaintiff must prove that the defendant's racketeering conduct caused her injury. 18 U.S.C. § 1964(c); Holmes v. Sec. Inv'r Prot. Corp., 503 U.S. 258, 268 (1992) (interpreting section 1964(c)'s language to mean that a RICO plaintiff must show both but-for and proximate causation to establish standing). As we have already noted, physicians can -- and do -- lawfully prescribe prescription drugs for off-label uses, even though the manufacturer is barred by law from promoting such prescriptions. See Lawton ex rel. United States, 842 F.3d at 128 n.4. So for any given prescription in this case, one would reasonably ask whether Forest's efforts to profit by illegally marketing drugs for pediatric use caused a particular prescription to be made, or whether, instead, the doctor wrote a given prescription based on his or her own professional medical judgment (perhaps reasoning that what works for an adult patient might also work for a younger patient).

Forest therefore urges that, even if we disagree with the district court on the issue of injury/efficacy, we should still

affirm the entry of summary judgment due to Painters' lack of proof of but-for causation. While the district court did not consider the issue of causation in its summary-judgment ruling, it did earlier assay Painters' causation evidence in ruling on Painters' motion for class certification. The district court labeled the proof so "insubstantial" and "fundamentally flawed" "as to preclude class certification." Painters I, 315 F.R.D. at 126–28. Forest would have us interpret these pronouncements as a finding that the evidence was insufficient as a matter of law to prove but-for causation.

We disagree. In the first place, it is unclear why the district court gauged the substantiality or merit of plaintiffs' proof in the context of a Rule 23 motion. The central issue in that context is not whether the method of proof would or could prevail. Rather, it is whether the method of proof would apply in common to all class members. See, e.g., Tyson Foods, Inc. v. Bouaphakeo, 136 S. Ct. 1036, 1047 (2016) ("When . . . 'the concern about the proposed class is not . . . some fatal dissimilarity but, rather, a fatal similarity -- [an alleged] failure of proof as to an element of the plaintiffs' cause of action -- courts should engage that question as a matter of summary judgment, not class certification.'" (alteration in original) (quoting Richard A. Nagareda, Class Certification in the Age of Aggregate Proof, 84 N.Y.U. L. Rev. 97, 107 (2009))).

More substantively, Painters' evidence does not seem clearly insufficient. There is ample evidence that Forest spent money inducing doctors to prescribe its drugs to pediatric patients and that it would not have done so had the effort not been worth the money. Two experts, Dr. Meredith Rosenthal and Dr. Christopher Baum, also opined that Forest's spending on promotions in general correlated positively with sales. As the district court pointed out, Painters' experts then assumed that this same approximate correlation applied to off-label promotional spending and off-label sales. Painters I, 315 F.R.D. at 127. The district court thought this assumption to be a "fundamental flaw" in the analysis. Id. Why, exactly, we are not sure. After all, why would Forest, which knew its markets better than anyone, have spent money on off-label marketing over the long term if it generated lower returns than would additional spending on less risky, lawful marketing? Certainly there is room for reasonable disagreement on the merits of Dr. Rosenthal and Dr. Baum's assumption.

If the jury accepts this assumption as reasonable, and if it finds that the prescriptions that Painters paid for were typical of those that the experts analyzed, jurors would then have a fair path to finding that Forest's off-label marketing caused Painters to pay for ineffective drugs. The experts' interpretation of the data indicated that Forest's off-label promotions caused

76% and 54% of all pediatric prescriptions of Celexa and Lexapro, respectively. Dr. Rosenthal estimated that if Painters paid for as few as five independent prescriptions, there would be a 98% chance that at least one was the result of off-label marketing. In fact, Painters likely paid for the Celexa or Lexapro prescriptions of more than five different patients.[8] So the odds that Painters was not harmed if the drugs were, indeed, ineffective was likely infinitesimal (assuming the prescriptions were independent of one another).[9]

[8] In its summary judgment order, the district judge observed that Painters reimbursed sixteen of its pediatric insureds for seventy-two off-label prescriptions of Celexa from 1999 through 2004, and thirty-one of its pediatric insureds for 234 off-label prescriptions of Lexapro from 2002 through early 2015. Painters III, 289 F. Supp. 3d at 251. It is not clear from the record how many of these Lexapro prescriptions were written prior to March 2009. Viewing this evidence in the light most favorable to Painters, Ellis v. Fidelity Mgmt. Tr. Co., 883 F.3d 1, 3, (1st Cir. 2018), and without any counter-argument on this point by Forest, we assume for purposes of this appeal only that well more than five of the aforementioned Lexapro prescriptions were filled prior to the FDA's 2009 approval of Lexapro.

[9] The statistical proof in this instance is being used only to prove that a group of prescriptions likely includes at least one that a certain activity caused, and it is then being utilized to estimate the percentage of such causally connected prescriptions in that group. Painters proposes no use of the statistical data to prove that Forest's off-label marketing caused any particular prescription to be written. See In re Asacol Antitrust Litig. (Asacol), 907 F.3d 42, 54 (1st Cir. 2018) (finding it "far from self-evident" that expert testimony opining that "ninety percent of class members were injured" would be "sufficient to prove that any given individual class member was injured").

Nor is Painters' evidence limited to the thrust of its statistics. Painters also has evidence that Forest sales representatives called or visited at least two physicians who subsequently ordered pediatric prescriptions of Celexa and Lexapro that Painters reimbursed. In addition, Painters produced evidence suggesting that Forest specifically targeted Painters' pharmacy-benefits manager, Prime, and that Prime relied upon a misleading report by Forest of Study MD-18 in managing Painters' formulary. All together, this is surely enough to raise a triable issue of fact as to whether Forest's off-label marketing caused Painters to pay for a prescription for which it would not have otherwise paid.

This is not to say that Painters will ultimately prevail on the issue of causation. The district court has not conducted a Daubert analysis. And there may be other potential bones to pick with the sufficiency of Painters' proof of causation. As the record now stands, though, we agree with Painters that we cannot affirm the summary judgment finding that its causation proof is insufficient as a matter of law.

As for Ramirez, Forest did not challenge her standing on the basis of causation in its memorandum in support of its motion for summary judgment. Accordingly, we express no opinion as to whether Ramirez has raised a triable issue on RICO causation. See Rosaura Bldg. Corp. v. Municipality of Mayagüez, 778 F.3d 55, 63

(1st Cir. 2015) ("Time and time again we have held that arguments not advanced before the district court are waived.").

As for proximate causation, it is of no moment that pediatricians were the immediate target of Forest's fraudulent marketing. Here, as in Kaiser, a jury could find that Painters and Ramirez were "the primary and intended victims of [Forest's] scheme to defraud." Kaiser, 712 F.3d at 37 (quoting Bridge v. Phx. Bond & Indem. Co., 553 U.S. 639, 650 (2008)). Moreover, Painters' and Ramirez's alleged harm (i.e., reimbursing or purchasing more pediatric prescriptions than they otherwise would have) was a "foreseeable and natural consequence" of Forest's scheme. Bridge, 553 U.S. at 658. Indeed, it was precisely the point.

Accordingly, for the foregoing reasons, we reverse the district court's entry of summary judgment for Forest on Painters' RICO and state-law claims and on Ramirez's RICO and unjust-enrichment claims.

III.

Early on in this litigation the district court denied Painters' motion to certify this case as a class action under Federal Rule of Civil Procedure 23(b)(3). In so ruling, the district court reasoned that a variety of important issues, including causation and injury, would pose individual questions that would need to be answered for each class member. Painters I,

315 F.R.D. at 123–30. The presence of these individual questions, reasoned the district court, defeated Painters' effort to satisfy the requirement of Rule 23(b)(3) that common issues must predominate. Id. Painters now appeals that ruling as it applies to classes consisting of third-party payors ("TPP") who paid for or reimbursed prescriptions of Celexa or Lexapro prior to early 2009. It is not clear why those issues to which the district court pointed would preclude certification of such a class. As we have already explained, Painters' clinical and statistical evidence, if believed, could establish causation and injury at least for any TPP who paid for more than a handful of different patients' prescriptions. Nevertheless, as we will explain, it has become apparent that the proper application of the statute of limitations, while preserving plaintiffs' individual claims, precludes Painters' attempt to maintain a class action.

A.

The parties agree that the applicable statutory limitations period is four years. See Agency Holding Corp. v. Malley-Duff & Assocs., Inc., 483 U.S. 143, 156 (1987). That four-year period began to run "at the time [the] plaintiff knew or should have known of his injury." Lares Grp., II v. Tobin, 221 F.3d 41, 44 (1st Cir. 2000) (citing Rodriguez v. Banco Central, 917 F.2d 664, 665 (1st Cir. 1990)). The injury here is the payment made on account of off-label prescriptions that Forest induced.

See Kaiser, 712 F.3d at 39 ("[E]conomic injury occur[s] when [plaintiff] paid for fraudulently induced [drug] prescriptions."). So, the key question becomes: By what date can we say, as a matter of law, that Painters knew or should have known that Forest was promoting the off-label, ineffective use of Celexa or Lexapro?

The district court found that date to be no later than March of 2009. In re Celexa & Lexapro Mktg. & Sales Practices Litig., 65 F. Supp. 3d 283, 289 (D. Mass. 2014). In February of that year, the United States unsealed its complaint against Forest in United States ex rel. Gobble, which detailed in thirty-three pages how "Forest engaged in a fraudulent scheme to market and promote Celexa . . . and Lexapro . . . off-label to treat depression and other psychiatric conditions in pediatric patients." Complaint at 2, United States ex rel. Gobble, No. 03-10395-NMG (D. Mass. Feb. 13, 2009), ECF No. 61 [hereinafter United States' Complaint]. Within weeks, two private class-action complaints followed, one in New York and another in Missouri, each also alleging a fraudulent scheme to market Celexa and Lexapro for ineffective, off-label uses. See Class Action Complaint, Universal Care, Inc. v. Forest Pharm., Inc., No. 09-cv-11518-NMG (D. Mass. Mar. 20, 2009), ECF No. 1; Class Action Complaint, N.M. UFCW Union's & Emp'rs' Health & Welfare Tr. Fund v. Forest Labs., Inc., No. 09-cv-11524-NMG (D. Mass. Mar. 12, 2009), ECF No. 1. Painters never argued before the district court that it was unaware

of the United States' complaint or the March 2009 lawsuits. Nor does it so argue on appeal. Rather, it argues that the lawsuits did not provide enough notice that Forest had been promoting the off-label use of Celexa and Lexapro. Such notice, Painters says, was not available until Forest's own public admission to that effect in November 2010, when it both pleaded guilty to criminal violations of the FDCA and entered into a civil settlement agreement with the United States.

Not surprisingly, Painters points to no case law holding that a statutory limitations period does not start to run until the potential defendant first delivers a gift-wrapped admission of its alleged wrongdoing. Were that the rule, very few limitations periods would ever commence, much less conclude. Instead, as we have explained in an analogous context, "[w]e look first to whether sufficient facts were available to provoke a reasonable person in the plaintiff's circumstances to inquire or investigate further. . . . Once a duty to inquire is established, the plaintiff is charged with the knowledge of what he or she would have uncovered through a reasonably diligent investigation." McIntyre v. United States, 367 F.3d 38, 52 (1st Cir. 2004); see also Sanchez v. United States, 740 F.3d 47, 52 (1st Cir. 2014) ("The discovery rule incorporates an objective standard. To delay commencement of the running of the statute of limitations, 'the factual basis for the cause of action must have been inherently

unknowable, [that is, not capable of detection through the exercise of reasonable diligence] at the time of injury.'" (alteration in original) (quoting Gonzalez v. United States, 284 F.3d 281, 288–89 (1st Cir. 2002))). The same fundamental principle applies to RICO suits. See Rotella v. Wood, 528 U.S. 549, 555 (2000) ("Federal courts . . . generally apply a discovery accrual rule when a statute is silent on the issue, as civil RICO is here. . . . [D]iscovery of the injury . . . is what starts the clock." (citations omitted)); Koch v. Christie's Int'l PLC, 699 F.3d 141, 150–51 (2d Cir. 2012) (noting that a RICO claim does not accrue until a plaintiff has "actual or inquiry notice of the injury" (quoting In re Merrill Lynch Ltd. P'ships Litig., 154 F.3d 56, 60 (2d Cir. 1998))).

We agree with the district court that the unsealing of the United States' complaint and the subsequent lawsuits filed in March 2009 were more than sufficient to put a TPP like Painters on notice that Forest had likely been inducing off-label prescriptions of Celexa and Lexapro. The United States' complaint chronicled how Forest suppressed a negative study on Celexa while promoting a positive study (which conveniently neglected to mention the earlier, negative study). United States' Complaint at 3, 14. The complaint quoted internal Forest communications and recounted the precise details of Forest's unlawful promotional activities. Id. at 15–22. It quoted Forest's physician-call notes

reporting on the efforts of Forest's sales representatives to promote the pediatric use of the drugs. E.g., id. at 20 ("[F]ocus on Lexapro efficacy at just 10 mg., great choice for child/adolescents."). It also named Forest marketing executives, e.g., id. at 23, and outside physicians involved in the promotion campaigns, e.g., id. at 21–22. It is inconceivable that any TPP like Painters would not have found in the complaint a very strong probability that Forest had systematically and fraudulently pushed its drugs on unsuspecting children.

Nevertheless, we also agree with the district court that Painters survived Forest's statute-of-limitations defense because the running of the limitations period was stayed for more than eight months by the filing of the N.M. UFCW class action in March 2009. See In re Celexa & Lexapro Mktg. & Sales Practices Litig., 65 F. Supp. 3d at 291. Painters was a member of the putative RICO class action for which the N.M. UFCW complaint sought certification. Under American Pipe & Construction Co. v. Utah, 414 U.S. 538 (1974), the limitations period during which Painters might sue on its own behalf was therefore tolled until the N.M. UFCW class action was dismissed in June 2010. Forest did not cross appeal the district court's application of American Pipe. Rather, Forest argues only that the limitations period began running long before March of 2009 when plaintiffs first should have suspected that Celexa and Lexapro were ineffective for pediatric use. We

reject that argument because the injury here is paying for unlawfully induced off-label prescriptions, not merely physician-directed, off-label prescriptions.

B.

Even though plaintiffs can sue, thanks to American Pipe, Painters cannot parlay that dispensation into the much-delayed filing of a class action. See China Agritech, Inc. v. Resh, 138 S. Ct. 1800 (2018). In American Pipe, the Supreme Court held that the "commencement of [a putative class action] tolls the running of the statute for all purported members of the class who make timely motions to intervene after the court has found the suit inappropriate for class action status." 414 U.S. at 552-53. China Agritech clarified that this tolling rule has limits: While a putative class member may join an existing suit or file an individual action upon denial of class certification, a putative class member may not commence a class action anew beyond the time allowed by the untolled statute of limitations. 138 S. Ct. at 1807 ("The 'efficiency and economy of litigation' that support tolling of individual claims do not support maintenance of untimely successive class actions; any additional class filings should be made early on, soon after the commencement of the first action seeking class certification." (citation omitted) (quoting Am. Pipe, 414 U.S. at 553)).

Painters argues that China Agritech is distinguishable from the case at hand because there was no substantive ruling on class certification in N.M. UFCW; the first time any district court addressed class certification was in Painters' case. Painters' position relies on an impermissibly narrow reading of the Court's decision in China Agritech. Though the Supreme Court granted certiorari in that case to answer the narrow question of whether a putative class member may commence a class action beyond the limitations period upon the district court's denial of a request for class certification filed within the statute of limitations, id. at 1804, the Court proceeded to provide a broader answer: Its precedents do not "so much as hint[] that [American Pipe] tolling extends to otherwise time-barred class claims," id. at 1806. Thus, the Court effectively ruled that the tolling effect of a motion to certify a class applies only to individual claims, no matter how the motion is ultimately resolved. To hold otherwise would be to allow a chain of withdrawn class-action suits to extend the limitations period forever.

For the foregoing reasons, the district court did not abuse its discretion in declining to certify Painters' proposed nationwide class of TPPs.

IV.

Finally, Painters also takes issue with the district court's denial of its motion to compel Forest's supplemental

production of documents related to the MD-18 Study. This court reviews a district court's discovery decision for abuse of discretion, intervening "only upon a clear showing of manifest injustice, that is, where the lower court's discovery order was plainly wrong and resulted in substantial prejudice to the aggrieved party." Pina v. Children's Place, 740 F.3d 785, 791 (1st Cir. 2014) (quoting Dennis v. Osram Sylvania, Inc., 549 F.3d 851, 859 (1st Cir. 2008)).

Here, it is undisputed that Forest did not perform an exhaustive search in response to Painters' requests for documents related to the MD-18 Study: Indeed, Forest acknowledges (employing the passive voice) that "files within the custody of the Clinical Supply Group were not searched." Forest also does not deny that its own preliminary search within this group -- after discovery had closed -- produced two responsive memoranda regarding the packaging error in the MD-18 Study. The only excuse Forest provides is that "[p]laintiffs were fully apprised of the scope of document collection and were aware that files within the custody of the Clinical Supply Group were not searched." Forest, however, points us to nothing in the record demonstrating that Painters acquiesced to Forest's limiting the scope of its document collection in this way. These admissions notwithstanding, the district court denied Painters' Rule 37 motion to compel the supplementary production of documents related to the MD-18 Study.

It reasoned that the Rule 26(e)(1) duty to supplement only applies when "the supplemental material has not been otherwise made known to the requesting party" and observed that Painters had already received "substantial production of documents related to the packaging error" such that any new production would be cumulative. Painters II, 288 F. Supp. 3d at 487.

Rule 26(e)(1) requires that a party who has responded to a request for production supplement its response in a timely manner "if the party learns that in some material respect the . . . response is incomplete . . . and if the additional . . . information has not otherwise been made known to the other parties during the discovery process." Fed. R. Civ. P. 26(e)(1). Whether or not "information has not otherwise been made known" -- and, thus, whether or not additional production would be cumulative -- necessarily hinges on the relevance that the additional production might have for the requesting party's claims and the complexity of the issue that the factfinder is tasked to resolve; clearly, a relatively high degree of granularity in document production is to be expected in technical matters of great significance to a party's overall claim.

The district court viewed FDA approval as being preclusive as to the validity of Studies MD-18 and MD-32. See Painters III, 289 F. Supp. 3d at 255–56. It also viewed the validity of those two studies as fatal to plaintiffs' attempt to

prove ineffectiveness with the type of evidence used in Neurontin. See id. Given those views, the district court understandably decided that further evidence on the question of effectiveness was cumulative and of no material import. See Painters II, 288 F. Supp. 3d at 487. Because we have now explained why the FDA's approval of Lexapro for its use in adolescents is not as preclusive as the district court might have reasonably thought, and because Painters and Ramirez have a live claim on the merits, one might reasonably expect Forest to search for responsive files within the "Clinical Supply Group." Accordingly, we vacate the district court's discovery ruling so that on remand it can consider whether further discovery is called for in view of our decision in this appeal.

V. Conclusion

For the foregoing reasons, we reverse the district court's entry of summary judgment for Forest on Painters' and Ramirez's RICO and state-law claims and vacate the district court's denial of Painters' Rule 37 motion to compel supplemental discovery. At the same time, we affirm the district court's denial of Painters' motion for class certification. We award no costs to any party.