United States Court of Appeals for the Fifth Circuit

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Fifth Circuit
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Lyle W. Cayce
Clerk

No. 23-30323

TINA HICKEY; HILDA ADAMS; GLORIA J. COOPER; CAROL R. WOODSON,

Plaintiffs—Appellees,

versus

HOSPIRA, INCORPORATED; HOSPIRA WORLDWIDE, L.L.C., *formerly known as* HOSPIRA WORLDWIDE, INCORPORATED; ACCORD HEALTHCARE, INCORPORATED,

Defendants—Appellants.

Appeal from the United States District Court
for the Eastern District of Louisiana
USDC Nos. 2:16-CV-17583, 2:16-MD-2740,
2:17-CV-12674, 2:18-CV-194,
2:18-CV-4731

Before WIENER, HAYNES, and HIGGINSON, *Circuit Judges*.

PER CURIAM:

The question before us is whether federal law preempts Plaintiffs' state law failure-to-warn claims against Defendant drug manufacturers. The district court held that it did not and denied Defendants' motion for summary judgment. For the reasons that follow, we VACATE the district

court order denying summary judgment and REMAND for further consideration of one outstanding issue discussed below.

I. Background

We start this section with some background on the relevant statutory framework. Then we describe the facts particular to this appeal. Finally, we explain the procedural posture.

A. Statutory Background

Under the Food, Drug, and Cosmetics Act ("FDCA"), 21 U.S.C. §§ 301–99i, a drug manufacturer must obtain approval from the Food and Drug Administration ("FDA") before selling its drug in the United States. 21 U.S.C. § 355(a). "[A] manufacturer seeking federal approval to market a new drug must prove that it is safe and effective and that the proposed label is accurate and adequate." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 612 (2011) (citations omitted). "Meeting those requirements involves costly and lengthy clinical testing." *Id.* (citations omitted). "Originally, the same rules applied to all drugs." *Id.* But the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (the "Hatch-Waxman Amendments") changed that. *See id.* The public policy behind the Hatch-Waxman Amendments was to "allow[] manufacturers to develop generic drugs inexpensively, without duplicating the clinical trials already performed on the equivalent brand-name drug." *Id.* This was done to assist patients in being able to afford the drugs. Now, under the law, there are three primary routes through which a manufacturer can obtain approval of drugs.

The method for approval of a brand new drug is laid out in § 505(b)(1)[1] of the FDCA. *See* 21 U.S.C. § 355(b)(1). It requires manufacturers to file a New Drug Application ("NDA"), which includes, inter alia, "full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A)(i). The first drug of a specific kind to be approved under § 505(b)(1) is called the Reference Listed Drug ("RLD"). Thereafter, other manufacturers who want to prepare the same drug or a drug that is similar enough may use two abbreviated pathways to obtain FDA approval with less burden and expense.

One such pathway is § 505(j), which permits the manufacturer of a generic drug to submit an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355(j). With limited exceptions, the generic drug must have the same active ingredients, route of administration, dosage form, strength, and proposed labeling as the RLD. 21 U.S.C. § 355(j)(2)(A). Because a § 505(j) drug is the same as the RLD in these respects, the manufacturer may rely on the safety and efficacy data submitted in the RLD's NDA. *Id.*

The final path—the one at issue here—is § 505(b)(2), which is available for drugs that differ from the RLD in ways that are slight enough for the manufacturer to still rely on the RLD's safety and efficacy data. *See* 21 U.S.C. § 355(b)(2). "Th[e] § 505(b)(2) application need contain only that information needed to support the modification(s) of the listed drug." 21 C.F.R. § 314.54(a). Unlike § 505(j) drugs, § 505(b)(2) drugs are not required to use the exact same labeling as the RLD. *See* 21 C.F.R. § 314.54(a)(2).

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[1] The parties refer to this provision and its counterparts—§§ 505(b)(2) and (j)—by their location in the FDCA rather than their location in the United States Code. The parties agree that doing so is common practice. Accordingly, we will do the same.

When the FDA approves a new drug, it also approves the exact text that will be included in the drug's labeling. *Wyeth v. Levine*, 555 U.S. 555, 568 (2009) (citing 21 U.S.C. § 355). "Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application." *Id.* But in some circumstances, the changes-being-effected ("CBE") regulation allows manufacturers to file a supplemental application with the FDA and simultaneously implement a labeling change before obtaining FDA approval. 21 C.F.R. § 314.70(c)(6).

The CBE regulation is available "'to add or strengthen a . . . warning' where there is 'newly acquired information' about the 'evidence of a causal association' between the drug and a risk of harm." *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 304–05 (2019) (ellipses in original) (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). The regulation defines "[n]ewly acquired information" as "data, analyses, or other information not previously submitted to the Agency," including but not limited to, "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 314.3(b).

We now turn to the facts specific to this case.

B. Factual Background

In 1996, the FDA approved Taxotere, the branded version of docetaxel, for the treatment of metastatic breast cancer. Taxotere is manufactured by Sanofi US Services Inc. and Sanofi-Aventis U.S. LLC (collectively, "Sanofi"). In 2004, the FDA also approved Taxotere as an adjuvant chemotherapy treatment for early-stage breast cancer. *See Earnest v. Sanofi U.S. Servs., Inc. (In re Taxotere (Docetaxel) Prods. Liab. Litig.)*, 26 F.4th 256, 260 (5th Cir. 2022). Once Sanofi's patent expired, Defendants

Hospira, Inc. and Hospira Worldwide, LLC (together, "Hospira") and Accord Healthcare, Inc. ("Accord") sought FDA approval under § 505(b)(2) to sell docetaxel. Defendants' applications relied on the FDA's findings of safety and effectiveness from Taxotere's NDA. Accord's docetaxel differs from Taxotere only in the inclusion of two inactive ingredients: citric acid and polyethylene glycol. Hospira's docetaxel differs from Taxotere only in that it involves a less concentrated formulation and a one-step, rather than two-step, dilution process. The FDA approved Hospira's application on March 9, 2011, and Accord's on June 8, 2011.

Accord's approved docetaxel label matched Taxotere's. Hospira's did too, except for the preparation-and-administration sections, due to the differences discussed above. Relevant to this case, as of 2011, the labels all included identical warnings about alopecia (a medical term for hair loss) as an adverse reaction and instructed doctors to explain that hair loss was one of the drug's most common side effects. The label did not state whether the hair loss could be permanent.

In March 2015, after oncology-patient advocates contacted the FDA to express concern that docetaxel was causing permanent, not just temporary, alopecia, the FDA sent Sanofi a request for its internal data regarding permanent alopecia. Sanofi produced 2,172 reports of alopecia generally, which included 117 reports of permanent alopecia, irreversible alopecia, or alopecia lasting longer than two years. Roughly 70% of the people who reported alopecia to Sanofi were taking docetaxel in combination with other chemotherapy agents with links to alopecia, and many reports concerned patients who also received hormonal therapies associated with alopecia. In October 2015, after reviewing Sanofi's submission, the FDA requested additional information and instructed Sanofi to update its label. *In re Taxotere (Docetaxel) Prods. Liab. Litig.*, 508 F. Supp. 3d 71, 78 (E.D. La. 2020).

In response to the FDA's request, Sanofi updated its label via the CBE regulation to add that "[c]ases of permanent alopecia have been reported." The FDA approved the update in December 2015. In approving the changes, the FDA stated that "the sponsor's simple statement that permanent cases have been reported is all that can reliably be said given the tremendous limitations of the data." In other words, the FDA did not conclude that the cases of permanent alopecia were necessarily caused by the docetaxel.

Three weeks later, Accord updated its label with the same changes via the CBE regulation, which the FDA approved in July 2016. In March 2017, Hospira also made similar changes via the CBE regulation, which the FDA approved in September 2017.

C. Procedural History

Plaintiffs in the underlying multidistrict litigation ("MDL") took docetaxel as part of their chemotherapy regimen for early-stage breast cancer and suffered permanent chemotherapy-induced alopecia ("PCIA"). Plaintiffs allege, inter alia, that Defendant manufacturers violated state law by failing to warn them that docetaxel could cause PCIA. Plaintiff Tina Hickey sued Hospira, and Plaintiffs Hilda Adams, Gloria J. Cooper, and Carol Woodson sued Accord. In 2016, Plaintiffs' suits were consolidated into MDL 2740 in the Eastern District of Louisiana. Our opinion only addresses the specifics related to these plaintiffs and these defendants. We understand that other actions filed by plaintiffs against defendants in the MDL may result in different outcomes.

Accord and Hospira moved for summary judgment on the basis that Plaintiffs' state law failure-to-warn claims are preempted by federal law. The district court denied both motions. Defendants then moved to certify the

order for interlocutory appeal, which the district court granted. Finally, we granted Defendants' request for permission to appeal.[2]

II. Jurisdiction & Standard of Review

The district court exercised diversity jurisdiction under 28 U.S.C. § 1332.[3] We have jurisdiction under 28 U.S.C. § 1292(b) because the district court certified its order for interlocutory appeal.

"Under 28 U.S.C. § 1292(b), a grant or denial of summary judgment is reviewed de novo, applying the same standard as the district court, but review only extends to controlling questions of law." *Castellanos-Contreras v. Decatur Hotels, LLC*, 622 F.3d 393, 397 (5th Cir. 2010) (en banc) (internal citations omitted). "The preemptive effect of a federal statute is a question of law that we review de novo." *Franks Inv. Co. v. Union Pac. R.R. Co.*, 593 F.3d 404, 407 (5th Cir. 2010) (en banc) (italics omitted).

III. Discussion

The question before us is whether federal law preempts Plaintiffs' state law failure-to-warn claims against Defendants. One way in which federal law preempts a state-law claim is when it is "impossible for a private

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[2] Sandoz, Inc., another defendant in the MDL, also moved for summary judgment. But the plaintiff against whom Sandoz moved purported to dismiss the suit against Sandoz after the district court certified its summary judgment order for interlocutory appeal. Sandoz contested the dismissal, but we dismissed Sandoz's petition for lack of jurisdiction.

[3] We requested a joint letter from the parties to address pleading deficiencies affecting the existence of diversity jurisdiction. Namely, the operative long-form complaint did not properly allege the citizenship of certain LLC defendants by failing to allege the citizenship of such defendants' members. The parties filed a joint letter addressing that issue. Because the parties have pointed to sufficient evidence in the record to establish "at least a substantial likelihood that jurisdiction exists," we grant their request to treat their joint letter as an amendment to the pleadings under 28 U.S.C. § 1653. *See Nadler v. Am. Motors Sales Corp.*, 764 F.2d 409, 413 (5th Cir. 1985). We conclude that diversity jurisdiction exists.

party to comply with both state and federal requirements." *Albrecht*, 587 U.S. at 303 (quotation omitted). In the failure-to-warn context, "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Mensing*, 564 U.S. at 620. Before reaching the merits, we address the parties' arguments concerning the applicable test for impossibility preemption in this context, the burden of proof, and the definition of "newly acquired information."

A. The applicable test

Defendants contend that it would have been impossible for them to comply with their alleged state law duties because they did not have "newly acquired information," as required to unilaterally update their labels via the CBE regulation. Plaintiffs respond that, under *Albrecht*, the relevant question for impossibility preemption is whether (1) Defendants "fully informed the FDA of the justifications for the warning required by state law," and (2) the FDA informed them that it "would not approve changing the drug's label to include that warning." 587 U.S. at 314. Defendants reply that whether the CBE regulation was even available to them is a threshold issue to *Albrecht*'s test. We agree with Defendants.

The Supreme Court has not addressed impossibility preemption in the § 505(b)(2) context, but its approach in other cases is nonetheless informative. In *Wyeth*, the Court first concluded that a § 505(b)(1) manufacturer (the original manufacturer of the relevant drug) had newly acquired information, thereby making the CBE regulation available; the Court then rejected the manufacturer's preemption argument in the absence of "clear evidence" that the FDA would not have approved the label changes. 555 U.S. at 569–70, 571–72.

Next, *Mensing* held that federal law preempted state law failure-to-warn claims against § 505(j) manufacturers (a subsequent manufacturer

making the exact same drug as the original manufacturer). 564 U.S. at 618. The Court accepted the FDA's interpretation of the CBE regulation as "allow[ing] changes to generic drug labels only when a generic drug manufacturer changes it label to match an updated brand-name label or to follow the FDA's instructions." *Id.* at 614. It then held that "the CBE process was not open to the Manufacturers for the sort of change required by state law." *Id.* at 615.

Albrecht returned to the § 505(b)(1) context, where the manufacturer "conceded that the FDA's CBE regulation would have permitted [it] to try to change the label," but argued for impossibility preemption on the basis that "the FDA would have rejected that attempt." 587 U.S. at 308–09. In response, the Court reiterated *Wyeth*'s requirement of "'clear evidence' that the FDA would not have approved the warning that state law requires." *Id.* at 310 (quoting *Wyeth*, 555 U.S. at 571). The Court announced that "clear evidence" requires a showing that "the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." *Id.* at 303.

In sum, *Mensing* did not reach the clear evidence test because the CBE regulation was not available to the manufacturers of the § 505(j) drug at issue, and the other two cases reached the clear evidence test but did so only after concluding that the CBE regulation was available (*Wyeth*) or after the manufacturer asserting preemption conceded its availability (*Albrecht*). Accordingly, we conclude that the availability of the CBE regulation is a threshold issue to the clear evidence test.[4]

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[4] Our sister circuits also treat the availability of the CBE regulation and the clear evidence test as two distinct steps in the analysis, albeit in the § 505(b)(1) context. *See, e.g.*, *Knight v. Boehringer Ingelheim Pharms., Inc.*, 984 F.3d 329, 338–41 (4th Cir. 2021) (holding

B. Burden of proof

The parties also disagree about who bears the burden of proof regarding the availability of the CBE regulation. Defendants agree with the approach adopted by the district court. The district court held that Plaintiffs bear the initial burden of producing information that the manufacturer could have used to modify the drug's label, but that Defendants bear the ultimate burden of proving that such information does not meet the requirements of the CBE regulation. Plaintiffs disagree with that approach and assert that the full burden of proving impossibility preemption rests with Defendants. Because the parties agree that Defendants bear the ultimate burden of proving that the information at issue does not meet the requirements of the CBE regulation, and because plaintiffs have already identified the information at issue, we need not decide which party bears the initial burden of producing the information at issue. We hold only that Defendants bear the ultimate burden of proving that the information at issue does not meet the requirements of the CBE regulation.

C. What constitutes "newly acquired information"

Defendants also argue that the district court erred by failing to enforce the requirement that newly acquired information must "reveal risks of a

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state law claim was preempted without applying clear evidence test because manufacturer did not have "newly acquired information" that would permit a labeling change via CBE); *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019) (treating availability of CBE regulation as threshold question to clear evidence test); *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 815 (7th Cir. 2018) (treating availability of CBE regulation and clear evidence test as separate inquiries that both must be satisfied); *Marcus v. Forest Lab'ys, Inc. (In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.)*, 779 F.3d 34, 41 (1st Cir. 2015) (treating availability of CBE regulation as threshold question to clear evidence test); *see also Perham v. GlaxoSmithKline LLC (In re: Zofran (Ondansetron) Prods. Liab. Litig.)*, 57 F.4th 327, 336–37 (1st Cir. 2023) (assuming without deciding that the availability of the CBE regulation is a threshold question to the clear evidence test).

different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 314.3(b).

Defendants' characterization of the district court's opinion appears to be correct. The district court first explained that the § 505(b)(2) pathway complicates the analysis of what constitutes newly acquired information. For example, even though § 505(b)(2) permitted Defendants to rely on Sanofi's safety and efficacy data when seeking approval, Defendants did not have a "right of reference" to that data during the relevant time period. *See* 21 U.S.C. § 355(b)(2). It is also undisputed that Defendants did not have access to Sanofi's adverse event reports during the relevant timeframe. Accordingly, the district court posited that "[w]ithout knowing the full extent of what was previously submitted to the FDA, Defendants could never determine whether information revealed risks of a different type or greater severity or frequency than included in previous submissions to the FDA." To avoid this result, the district court held that "any post-approval data or analysis that would have demonstrated that the warnings in Defendants' labels were insufficient would have qualified as newly acquired information under the CBE regulation." The district court then proceeded to analyze whether certain information revealed a causal relationship between docetaxel and PCIA, without regard to whether such data or analysis "reveal[ed] risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 314.3(b).

We agree with Defendants that the district court erred by failing to enforce the requirement that newly acquired information must "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." *Id.* Indeed, the district court approach puts the highest standard on secondary manufacturers rather than original ones, which does not comply with the overall framework. The district court relied on the FDA's response to a rulemaking comment in which the commenter

expressed concern that the "newly acquired information" requirement "might undermine warnings in situations where a sponsor warns about a particular risk, but then later information demonstrates that the warning was insufficient." *See* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49606 (Aug. 22, 2008). In response, the FDA stated:

> FDA believes that the final rule addresses this concern. First, if later data or analyses demonstrate that prior warnings were insufficient, such data would clearly qualify as newly acquired information under the rule. Indeed, the rule expressly provides that new analyses of previously submitted information are considered new information that could be submitted by a CBE supplement (*provided that other requirements for a CBE supplement are met*). Therefore, if a sponsor determined that existing warnings were insufficient based on newly acquired information such as a new analysis of previously submitted data, the sponsor could still submit a CBE based on its new analysis of the previous data, *provided the other requirements of the rule are met*.

Id. (emphasis added). Contrary to the district court's conclusion, the FDA's statement does not call for a departure from the textual definition of "newly acquired information." Instead, the statement twice clarifies that all requirements of the CBE regulation must be met before a manufacturer can unilaterally change its label. *Id.*

Nor do the district court's practical concerns justify a departure from the text. Neither Defendant contends that a § 505(b)(2) manufacturer can *never* identify newly acquired information that would support a labeling change via the CBE regulation. For example, the manufacturer of a § 505(b)(2) drug must submit its own safety and efficacy data concerning the differences between its drug and the RLD; therefore, it would be able to compare post-approval data related to such differences against its own

submissions to the FDA. *See* 21 C.F.R. § 314.54(a) ("[A] 505(b)(2) application need contain only that information needed to support the modification(s) of the listed drug."). Here, however, the differences between Defendants' docetaxel products and Taxotere are not alleged to cause PCIA, so the "difference" issue is not in play.

Turning to the general potential for permanent alopecia, Hospira acknowledged that "the pre- and post- approval scientific literature provided a basis for [Defendants] to compare and evaluate whether or not the 'new' information revealed a greater incidence of permanent hair loss." Likewise, Accord acknowledged that "if a manufacturer were to receive a measurable uptick in adverse event reports that reflected a 'greater severity or frequency' than the incidence rates conveyed by pre-approval literature," that could constitute newly acquired information.

We agree that because there was publicly available scientific literature (referred to hereafter as "scientific literature") on the drugs, there is something for these Defendants to review and be aware of and responsive to. Therefore, in this case, for post-approval information to meet the requirements of "newly acquired information," it must *at least* "reveal risks of a different type or greater severity or frequency" than the risks revealed in the scientific literature available to Defendants.[5] If it does not, Defendants

[5] After the FDA approved Taxotere, Sanofi was required to submit to the FDA publicly available scientific literature related to docetaxel as part of its pharmacovigilance duties. *See* 21 C.F.R. § 314.80(b)–(d); 21 C.F.R. § 314.81(b). Plaintiffs do not dispute that, before the FDA approved Defendants' drugs, Sanofi had an obligation to submit to the FDA the scientific literature discussed *infra* at § III.D.1. Accordingly, that scientific literature provides a baseline comparator for determining whether post-approval information "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA." *See* 21 C.F.R. § 314.3(b).

will have established impossibility preemption. We therefore turn to the relevant comparisons.

D. Whether Defendants had newly acquired information

The information at issue includes the scientific literature on the risk of docetaxel-induced PCIA and Hospira's adverse event reports.[6] Defendants argue that this information does not meet the definition of "newly acquired information" because it does not "reveal risks of a different type or greater severity or frequency" than the pre-approval scientific literature. 21 C.F.R. § 314.3(b).

1. Pre-approval scientific literature

We start with the pre-approval scientific literature that Defendants assert forms the baseline of our analysis.

i. The Nabholtz Study

In 2001, J.M. Nabholtz and others published a study on docetaxel and other chemotherapy drugs in the Journal of Clinical Oncology. Four out of fifty-four patients suffered from "long-lasting (longer than two years) partial alopecia," after being treated with docetaxel, in addition to other drugs. Defendants note that this constitutes a 7.4% incidence rate.

ii. The Sedlacek Study

In 2006, S.M. Sedlacek published a study in which seven out of 112 patients suffered from "persistent significant alopecia," or "hair regrowth less than 50% of the pre-chemotherapy amount of hair," after being treated with docetaxel, in addition to other drugs. The study concluded that "there

[6] It is undisputed that Accord did not receive any adverse event reports concerning PCIA during the relevant time period.

is a small but significant possibility of poor hair regrowth lasting up to 7 years." Defendants note that this study revealed a 6.3% incidence rate.

2. Post-approval scientific literature

Having set forth the pre-approval scientific literature, we now turn to the post-approval scientific literature to determine whether it "reveal[s] risks of a different type or greater severity or frequency." *Id.*

i. The Palamaras Letter

In March 2011, Dr. Ioulios Palamaras published a letter to the editor of the Journal of the American Academy of Dermatology discussing a retroactive chart study of patients at the author's hair clinic over a seven-year period. The Palamaras Letter identified seven cases of PCIA out of 8,430 patients with non-scarring alopecia. Of those seven patients, five had been treated with docetaxel. We agree with Defendants that the Palamaras Letter does not "reveal risks of a different type or greater severity or frequency" than the pre-approval scientific literature. *Id.*

ii. The Miteva Study

In June 2011, Dr. Mariya Miteva and others published a study in the American Journal of Dermatopathology. It concluded that "[p]ermanent alopecia after chemotherapy . . . has been increasingly reported in the past few years even if its prevalence and histological features are not well studied." Defendants argue that only six of the patients discussed in the study were treated with docetaxel and that the authors did not describe the size of the sample population from which those six patients were drawn, making the calculation of an incidence rate impossible. We agree with Defendants that the Miteva Study does not "reveal risks of a different type or greater severity or frequency" than the pre-approval scientific literature. *Id.*

iii. The Kluger Study

In 2012, N. Kluger and others published a study in the Annals of Oncology that analyzed the relationship between PCIA (defined therein as "incomplete hair regrowth at 26 months post-chemotherapy") and a sequential chemotherapy regimen of fluorouracil, epirubicin, cyclophosphamide (collectively, "FEC"), and docetaxel. The authors collected data on twenty women who developed PCIA between 2007 and 2011. Based on the results of the study, the authors "estimated that the incidence of [PCIA] in this patient population is ~2%." We hold that the Kluger Study did not "reveal risks of a different type or greater severity or frequency" than the pre-approval scientific literature. *Id.*

iv. The Tosti Letter

In 2013, Dr. Antonella Tosti and others (including Dr. Ioulios Palamaras) published a letter to the editor of the Journal of the American Academy of Dermatology. The authors stated that over the last four years they had "observed five patients with PCIA following high-dose docetaxel chemotherapy for breast cancer" (citing the Palamaras Letter) and noted that two other cases had been presented at the Royal Society of Medicine in London. We do not see how the Tosti Letter "reveal[s] risks of a different type or greater severity or frequency" than the pre-approval scientific literature. *Id.*

v. The Bertrand Abstract

In December 2013, M. Bertrand and others published an abstract for a presentation at the San Antonio Breast Cancer Symposium. It discussed a study of seventy-nine patients treated with FEC and docetaxel between 2005 and 2007. Five years after the end of treatment, twenty-six patients still experienced alopecia—twenty-one "minimal," two "moderate," and three "severe." The abstract did not define those terms. It also stated that the

patients with alopecia "were significantly older and more often postmenopausal than in the control group" and identified menopause as "a significant risk factor for developing alopecia."

Taking into account only moderate and severe cases, the incidence rate of alopecia five years after the end of treatment was 6.3% (five out of seventy-nine patients). That is the same as the Sedlacek study and less than the Nabholtz Study (7.4%). One issue that was not addressed in the district court is what the "minimal" cases were. If we include those, the incidence rate is higher than the pre-approval literature.[7] *Id.* Accordingly, we will remand on this point.

vi. Cumulative body of scientific literature

We next consider Plaintiffs' argument that the cumulative body of scientific literature meets the definition of newly acquired information.[8] Plaintiff primarily relies on *Wyeth*, which stated "that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Wyeth*, 555 U.S. at 569.

But *Wyeth* is distinguishable from the instant case. In *Wyeth*, the plaintiff presented evidence of twenty adverse incidents prior to her injury, the first of which the manufacturer reported to the FDA in 1967—after the

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[7] We also note that Hickey began taking docetaxel two months before publication of the Bertrand Abstract and finished treatment two months after its publication. Even if Hickey had stopped taking it once the information came out, she would have already taken a significant amount.

[8] To the extent Plaintiffs argue that an individual study that Sanofi was required to submit to the FDA before approval of Defendants' drugs independently constitutes "newly acquired information," we reject that argument. *See In re Celexa & Lexapro*, 779 F.3d at 41 ("[T]he line so drawn lets the FDA be the exclusive judge of safety and efficacy based on information available at the commencement of marketing, while allowing the states to reach contrary conclusions when new information not considered by the FDA develops.").

drug's initial approval. *Id.* at 561, 569. The Court held that as adverse incidents continued to occur, the manufacturer "could have analyzed the accumulating data and added a stronger warning." *Id.* at 570. Here, however, the scientific literature already indicated a 6.3% to 7.4% incidence rate of PCIA among patients taking docetaxel before the FDA approved Defendants' drugs. Although the post-approval scientific literature continued to reveal instances of docetaxel-induced PCIA, that is not enough—it must also "reveal risks of a different type or greater severity or frequency" than the pre-approval scientific literature. 21 C.F.R. § 314.3(b). We conclude that it did not, with the possible exception of the Bertrand Abstract, which we are remanding for further consideration.

3. Hospira's adverse event reports

Finally, we consider the adverse event reports that Hospira received during the relevant time period. Hospira received forty-three reports of PCIA through September 2016. Hospira argues that the reports do not constitute newly acquired information because forty-three incidents of PCIA out of the roughly 161,000 patients treated with Hospira's docetaxel during the relevant time period amounts to an incidence rate of 0.03%,[9] which is much lower than the incidence rates revealed by the Nabholtz and Sedlacek studies. We agree with Hospira that its adverse event reports do not "reveal risks of a different type or greater severity or frequency" than the pre-approval scientific literature. 21 C.F.R. § 314.3(b).

* * *

[9] In fact, Hospira points out that the true incidence rate is even lower than 0.03% because the numerator (forty-three) represents the number of adverse event reports through 2016 while the denominator (161,000) represents the number of patients treated with docetaxel through 2014.

Thus, we conclude that these particular Defendants did not have newly acquired information showing that PCIA occurred with any greater severity or frequency than before the approval of their drugs, with the possible exception of the Bertrand Abstract. Accordingly, we will only remand the question of the effect of the Bertrand Abstract results. If the analysis of the same shows that it is not sufficient, then these Defendants are not liable to these particular Plaintiffs on their state law failure-to-warn claims.

IV. Conclusion

For the reasons explained above, we VACATE the judgment on Plaintiffs' failure-to-warn claims and REMAND on the sole question raised above, following the rest of our analysis herein.