PUBLISHED

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 19-1636

CLAUDE R. KNIGHT; CLAUDIA STEVENS, individually and as Personal Representative of the Estate of Betty Erelene Knight; BETTY ERELENE KNIGHT, Deceased,

Plaintiffs - Appellees,

v.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Defendant - Appellant.

Appeal from the United States District Court for the Southern District of West Virginia, at Huntington. Robert C. Chambers, District Judge. (3:15-cv-06424)

Argued: October 29, 2020 Decided: January 6, 2021

Before NIEMEYER, DIAZ, and QUATTLEBAUM, Circuit Judges.

Reversed by published opinion. Judge Quattlebaum wrote the opinion, in which Judge Niemeyer and Judge Diaz joined.

ARGUED: Paul Schmidt, COVINGTON & BURLING LLP, Washington, D.C., for Appellant. James Darren Summerville, SUMMERVILLE FIRM, LLC, Atlanta, Georgia, for Appellees. **ON BRIEF:** Phyllis A. Jones, COVINGTON & BURLING LLP, Washington, D.C.; Adam H. Charnes, Thurston H. Webb, KILPATRICK TOWNSEND & STOCKTON LLP, Winston-Salem, North Carolina, for Appellant. C. Andrew Childers, Emily T. Acosta, CHILDERS SCHLUETER & SMITH, Atlanta, Georgia; Neal L. Moskow, URY & MOSKOW, LLC, Fairfield, Connecticut, for Appellees.

QUATTLEBAUM, Circuit Judge:

Under the preemption doctrine, a state-law challenge to federally approved pharmaceutical warning labels may only proceed when the pharmaceutical company has the unilateral ability to change that labeling. The Food and Drug Administration's changes-being-effected ("CBE") regulation permits pharmaceutical companies to unilaterally modify their physician labels only to "add or strengthen a . . . warning" based upon "newly acquired information" about "evidence of a causal association" between the drug and a risk of harm. 21 C.F.R. § 314.70(c)(6)(iii). Here we must determine some goalposts of "newly acquired information."

Boehringer Ingelheim Pharmaceuticals, Inc. developed a drug called Pradaxa to help reduce the risk of stroke. The FDA approved the drug and its label. After taking this drug for over a year, Betty Knight suffered a gastrointestinal bleed. She then developed other complications and eventually died. Her children, Claude Knight and Claudia Stevens,[1] sued Boehringer asserting a variety of state-law claims alleging Boehringer failed to adequately warn about the risks associated with taking Pradaxa.

Boehringer argued that federal law preempted the claims. The Knights disagreed, claiming the risks were "newly acquired information" discovered after Pradaxa's FDA approval. If true, then Boehringer could have added warnings to its physician label without FDA approval, and federal law would not preempt the state-law claims.

[1] For clarity, we will refer to Betty Knight as "Knight" and her children as the "Knights."

The district court agreed with the Knights and allowed the case to go to the jury. The jury returned a mixed verdict, finding for Boehringer on the Knights' failure to warn and breach of express and implied warranty claims, but for the Knights on their fraud claim. Boehringer filed a renewed motion for judgment as a matter of law, and, in the alternative, a new trial. After the district court denied its post-trial motions, Boehringer appealed on several grounds. Most relevant here, it argues it did not discover "newly acquired information" that would have permitted a unilateral change of Pradaxa's physician label. Thus, according to Boehringer, the Knights' fraud claim based on the physician label was preempted. Because we agree with Boehringer, we reverse the district court's order denying Boehringer's post-trial motion for judgment as a matter of law.

I.

Before addressing the preemption issues, we begin with some background on the development of Pradaxa and its approval by the FDA. We then describe Betty Knight's use of the drug, the events that gave rise to this case and the case's procedural history.

A.

Over two million Americans have atrial fibrillation ("AFib"), a condition that causes the heart to beat irregularly. This irregular heartbeat can lead to blood clots, which in turn can cause strokes. Therefore, many AFib patients take blood thinners to prevent clots and thus reduce the risk of stroke. But while blood thinners reduce the risk of stroke, they create other risks. One is the risk of uncontrollable, and potentially fatal, bleeding.

Before Pradaxa, the primary blood thinner on the market was warfarin.[2] Patients taking warfarin must regularly monitor blood concentration levels of the medication. Monitoring is needed because there is an optimal blood concentration range that applies to all patients. If the concentration level of warfarin in the blood exceeds that range, the risk of bleeding is too high. If the level is below that optimal range, the risk of clots and a stroke is too high. The monitoring helps ensure that blood concentration levels stay within the desired range. Alongside this monitoring, patients taking warfarin must comply with dietary and medication restrictions as its effectiveness is reduced by eating certain foods. Recognizing the market for an effective alternative that needs neither monitoring nor dietary restrictions, Boehringer developed Pradaxa.[3]

Boehringer's development of Pradaxa included a three-year study—known as the "RE-LY" study—involving over 18,000 patients. In it, Boehringer tested a 150 mg dose and a 110 mg dose of Pradaxa. The results showed that the 150 mg dose of Pradaxa prevented strokes more effectively than warfarin with no greater risk of bleeding. The 110 mg dose was no better than warfarin at preventing strokes but lowered the risk of bleeding.

[2] Pradaxa is Boehringer's brand name for the drug dabigatran, which is why it is capitalized. Warfarin, however, is the generic pharmaceutical name for the drug often sold under the brand names Coumadin or Jantoven. We follow the parties' lead in referring to these drugs as Pradaxa and warfarin, respectfully, for simplicity.

[3] Our decision should not be construed as an expression of support for Pradaxa as compared to warfarin. Warfarin, first approved in 1954, is an essential medicine according to the World Health Organization. *See* World Health Org., WORLD HEALTH ORGANIZATION MODEL LIST OF ESSENTIAL MEDICINES 34 (21st ed. 2019). Our discussion, rather, is simply to recount the background of Pradaxa's development and the rationales provided to the FDA.

Importantly, in analyzing its data, Boehringer did not find a Pradaxa blood concentration level for all patients that best balanced the risks and benefits of taking Pradaxa. Absent a target blood concentration level, Pradaxa did not require regular blood monitoring. Boehringer submitted a "new drug application" to the FDA for Pradaxa, which contained all its clinical data, including the RE-LY study.

In considering Boehringer's application, the FDA examined Boehringer's study and performed its own analysis. It concluded there was a "significant relationship" between Pradaxa blood concentration and bleeding events. J.A. 1172. Still, in 2010, the FDA approved the 150 mg dose. It did not approve the 110 mg dose, however, reasoning that it did not provide enough increased benefit. Consistent with Boehringer's analysis, the FDA approval did not require the blood monitoring required for warfarin.

The FDA also directed Boehringer to sell a 75 mg dose of Pradaxa for patients with severe kidney impairment. Because the kidneys eliminate Pradaxa from the bloodstream, patients with low kidney function face a greater risk of too much Pradaxa in their blood, which increases the chance of bleeding. But a lower dosage would mean less Pradaxa in the blood and, thus, less risk of bleeding.

As the FDA knew, Boehringer had not studied this 75 mg dose, or even studied Pradaxa in patients with severe kidney impairment. Its failure to do so was not because Boehringer did not appreciate the potential risk of Pradaxa to patients with kidney impairment. Rather, Boehringer was concerned with the medical ethics of such testing. Like Boehringer, the FDA did not test Pradaxa on kidney-impaired patients. Instead, from modeling Boehringer's clinical data, the FDA determined that 75 mg was an appropriate

dose for patients with severe kidney impairment, so that these patients could still reap Pradaxa's stroke-prevention benefits. The FDA cautioned Boehringer, however, that "there is no empirical data on this population with regard to bleeding risk," so "particular attention post-marketing should be paid to bleeding and other safety events" in those kidney-impaired patients treated with the 75 mg dose. J.A. 1412.

At the same time as its approval of the 150 and 75 mg doses, the FDA also approved a label for Pradaxa. The label had two parts: the physician label, which went to doctors, and the Medication Guide, which went to patients. Both documents contained warnings of bleeding. Relevant here, the physician label warned that "PRADAXA can cause serious and, sometimes, fatal bleeding" and that the "[r]isk of bleeding increases with age." J.A. 1253. It also stated that the "[m]ost common adverse reactions (>15%) are gastritis-like symptoms and bleeding." J.A. 1253. The Medication Guide similarly warned that "PRADAXA can increase your risk of bleeding because it lessens the ability of your blood to clot," and this risk was heightened for patients "over 75 years old." J.A. 1262.

Consistent with the FDA's instructions, both documents also contained information about the risk of bleeding for patients with kidney problems. The physician label indicated that the "dose of PRADAXA in patients with severe renal impairment" should be reduced to 75 mg, and, if kidney function fell below a certain threshold, Pradaxa was not recommended at all. J.A. 1256. And the Medication Guide warned that "[y]ou may have a higher risk of bleeding if you take PRADAXA and . . . have kidney problems." J.A. 1262.

After the FDA approved Pradaxa and its warnings, Boehringer's internal scientists continued to study the RE-LY data.[4] One of the questions they continued to study was whether a Pradaxa blood concentration range optimized the risk of bleeding with the benefit of stroke prevention for all patients. The preliminary results of the continued study began to emerge in the second half of 2011. During that time, Boehringer scientists began to work on a paper (eventually known as the "Reilly Paper") to describe their findings. The purpose of the paper was to "evaluate the correlations between plasma concentrations and efficacy and safety outcomes in [AFib] patients, and to identify factors affecting" Pradaxa blood concentration. J.A. 929. In other words, was there an optimal Pradaxa concentration range that might require regular monitoring?

As noted above, Boehringer's earlier analysis of its data revealed no such optimal range that applied to all patients. But Boehringer's continued study of the data used additional analytical approaches. The preliminary results of this continued study indicated there might be, contrary to Boehringer's earlier assessment, such an optimal range. Dr. Reilly, one of the lead scientists conducting the study, recognized that identifying such a range might compel Boehringer to require some testing to ensure a patient remained in that optimal range. He also recognized that Boehringer's marketing officials, who felt the lack of a monitoring requirement distinguished Pradaxa in the marketplace, might not like the preliminary results of the study. On August 1, 2011, he e-mailed a Boehringer executive

[4] At least one impetus for this continued study, according to a lead Boehringer scientist, was that once Boehringer had "a competitor" with a drug "as good as" Pradaxa, Boehringer "will be looking for ways to make [Pradaxa] better." J.A. 510.

that he was "aware that the conclusions that appear to emerge from this paper are not the ones currently wished for by marketing (that dose adjustment will optimize therapy) . . . ." J.A. 510. But Dr. Reilly made clear that the initial findings were not final. Continuing with the email, he explained that he wanted to "just see where this paper ends up." J.A. 510.

In November 2011, Boehringer revised the physician label pursuant to the CBE regulation permitting unilateral modification of physician labels to "add or strengthen a . . . warning" based upon "newly acquired information." 21 C.F.R. § 314.70(c)(6)(iii). The revised label disclosed that "[p]atients with severe renal impairment were not studied in RE-LY. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling." J.A. 1286. It also warned that "impaired renal function" is a "major" cause of heightened Pradaxa blood concentration levels, J.A. 1283, and recommended "assess[ing] renal function prior to initiation and, in patients" with kidney impairment or old age, at least once a year. J.A. 1281.

In December 2011, Boehringer scientists shared a draft version of the paper within the company. Consistent with Dr. Reilly's August 1, 2011, email, the draft found that kidney function was the most important determinant of Pradaxa blood concentration and that "[b]oth safety and efficacy of [Pradaxa] are related to" its concentration. J.A. 926–27. It concluded that "[a]n optimal balance between benefit and risk occurs in the range of concentrations between 40 and 215 ng/mL," and that "less than 20% of patients would be expected" to fall outside that range. J.A. 927, 937. Reflecting the concern Dr. Reilly raised, some Boehringer officials opposed publication of this paper because of its potential conflict

with Boehringer's marketing message that no testing to monitor blood concentration was required for patients taking Pradaxa.

Boehringer continued to analyze the data and work on the paper. A year and a half later, in June 2013, it submitted the finalized paper for publication. The final version mirrored the draft version with one major exception: it did not conclude there was an optimal therapeutic blood concentration range for all patients. Instead, it concluded that kidney function was probably the most predictive factor of Pradaxa blood concentration levels, and that the risk of stroke falls and the risk of bleeding rises in correlation with such concentration levels.

B.

With that background of Pradaxa, we now turn to the facts involving the Knights. In October 2011, Knight, eighty-five years old at the time, visited her primary care doctor with her children. Knight suffered from multiple medical problems, including prior strokes, a previous heart attack, congestive heart failure, coronary artery disease, COPD, hypertension, diabetes, anemia, dementia and chronic kidney disease. She also suffered from AFib for which she took warfarin. She disliked warfarin's dietary restrictions and monthly blood-monitoring requirements, so she inquired about switching to Pradaxa. At the visit, her provider prescribed a 75 mg Pradaxa dose.[5]

[5] Unfortunately, our record is unclear as to who initially prescribed Pradaxa to Knight. Although one of Knight's providers, Dr. MacFarland, testified it was her "general practice" to "go over risks and benefits" when prescribing a new medication, there is no evidence in the record that Dr. MacFarland met with Knight in October 2011. J.A. 1632. She did sign the Prior Authorization Form for insurance purposes after Knight's

For a year and a half, Knight continued to take Pradaxa without incident. But in April 2013, she suffered a heart attack, after which doctors placed a stent in her heart and prescribed her new medications to prevent heart attacks. But the new medications, like Pradaxa, increased the risk of bleeding. Still, her doctors kept her on Pradaxa.

The next month, Knight suffered a serious bleed in her colon. Her health did not improve in the next several months. Although she did not suffer another bleed, Knight was admitted to the hospital several times for various health issues. She died in September 2013 after another heart attack.

C.

Knight's children, individually and as representatives of Knight's estate, sued Boehringer in the Southern District of West Virginia. They asserted claims for strict liability failure to warn, negligent failure to warn, breach of express warranty, breach of implied warranty and fraud. All the claims rested on the allegation that Boehringer failed to properly warn that Pradaxa created a heightened risk in certain patients for serious bleeding and that this led to Knight's death.

During a three-week trial, the Knights focused on the Medication Guide's alleged failure to warn Knight that Pradaxa could cause bleeding and that the 75 mg dose was never tested in patients, even though these risks were disclosed in the physician label as of

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appointment in her office, but she does not specifically remember seeing Knight at that time. And according to Boehringer, it was a nurse practitioner in Dr. MacFarland's office who initially prescribed Pradaxa to Knight, but she was never deposed. *See* Appellant's Br. at 11; Reply Br. at 12 n.4.

November 2011. At the end of the Knights' case, Boehringer moved for judgment as a matter of law on all claims, arguing that federal law preempts any claim based on alleged misstatements or omissions in the Medication Guide. The district court did not rule on the motion at that time, but, at the end of the trial, granted the motion in part, holding "that any claim by the plaintiffs that the Medication Guide should be modified to include the warnings or statements that plaintiff has proffered is pre-empted." J.A. 1712. Central to the court's decision was the fact that Boehringer, by law, cannot change the Medication Guide without FDA approval.

The court denied the remainder of the motion and did not dismiss any specific claims. It concluded that claims based on the physician label were not preempted. Unlike the Medication Guide, which went to patients, the physician label went to doctors. The court reasoned that the physician label can be modified without FDA approval to "add or strengthen a . . . warning" based upon "newly acquired information" about evidence of a causal association between the drug and a risk of harm. J.A. 1456 (quoting 21 C.F.R. § 314.70(c)(6)(iii)). It also noted that, although Knight never saw the physician label, West Virginia law allows claims based on indirect reliance on a doctor's advice, which is based upon the physician label. *See Roney v. Gencorp*, No. 3:05-0788, 2009 WL 3073973, at *2 (S.D.W. Va. Sept. 18, 2009).

The jury returned a mixed verdict, finding for Boehringer on all claims except fraud. The jury found that Knight would not have taken Pradaxa absent the fraud, and the drug proximately caused her injuries, but not her death. It awarded the Knights $250,000 in compensatory damages and $1,000,000 in punitive damages.

Boehringer renewed its motion for judgment as a matter of law under Federal Rule of Civil Procedure 50(b), and, in the alternative, a new trial, arguing the fraud claim was preempted and the verdict inconsistent.[6] The district court denied the motions. It held the fraud claim was not preempted because, even though claims based on the Medication Guide were preempted, the Knights had introduced evidence Boehringer had "newly acquired information" which would have permitted it to unilaterally change the physician label pursuant to the CBE regulation. Additionally, it found that, although there was no evidence Knight read the physician label, there was evidence that her doctor reviewed it and that Knight indirectly relied on that label through her doctor. Boehringer timely appealed.

[6] The district court held that Boehringer waived any objection to the inconsistent verdict because it was a general verdict with special questions under Federal Rule of Civil Procedure 49(b), which requires a contemporaneous objection. Boehringer challenges this holding on appeal, but we do not reach the issue because we reverse on preemption grounds.

II.

Our central issue on appeal is whether the Knights' fraud claim is preempted.[7] Preemption is a question of law, which we review de novo. *Epps v. JP Morgan Chase Bank, N.A.*, 675 F.3d 315, 320 (4th Cir. 2012).[8]

In this context, federal preemption occurs when it is "impossible for a private party to comply with both state and federal requirements." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019). "The underlying question . . . is whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." *Id.* at 1677–79. A state law challenge to FDA-approved warnings, including a tort action under state law, can thus

[7] Boehringer also challenges the sufficiency of reliance evidence presented. The record does not establish that Dr. MacFarland met with Knight when she was first prescribed Pradaxa, and there is no other provider in the record who testified to warning Knight about Pradaxa's risks. And Knight's children, who were present at the appointment when Knight was first prescribed Pradaxa, either do not remember the meeting at all or remember receiving no warnings about the drug. J.A. 1679 ("She didn't question us or—or tell us anything else about the drug."). The Knights' evidence on this issue is that Dr. MacFarland customarily advises her patients of the disclosed risks of a drug. While Boehringer's argument is compelling, we need not address it as we decide the case solely on preemption grounds.

[8] From the portions of the record provided to us, it is unclear whether the district court decided the "newly acquired information" question itself or considered it a fact question for the jury. Regardless, we appreciate that the district court did not have the benefit of the Supreme Court's decision in *Albrecht*, which clarifies that "a judge, not the jury, must decide the pre-emption question." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1676 (2019). For that reason, Boehringer's statement at trial that "there's probably a fact issue on whether there's newly acquired information" was made before *Albrecht* was decided and thus carries no weight. J.A. 1711.

proceed only when the defendant had the unilateral ability to change that labeling; otherwise, the claim is preempted.

Under FDA regulations, companies cannot unilaterally change the Medication Guide without prior FDA approval because doing so is considered a "major" change. *See* 21 C.F.R. § 314.70(b) (explaining that "any change to a Medication Guide" requires "supplement submission and approval prior to distribution of the product made using the change"). But companies can change the physician label under the CBE regulation "if the change is designed 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." *Albrecht*, 139 S. Ct. at 1673 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)).

That brings us to the heart of this case. The Knights allege a labeling deficiency—the absence of a recommendation that patients with impaired kidney function taking Pradaxa undergo blood testing to check Pradaxa concentration levels. But did Boehringer have "newly acquired information" as defined in the CBE regulation that could have justified a unilateral change in the Pradaxa physician label?

A.

To answer that question, we begin with the definition of "newly acquired information." Newly acquired information "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." 21 C.F.R. § 314.3(b). Importantly, "newly acquired information is not limited to new data, but also encompasses new analyses of previously submitted data." *Wyeth v. Levine*, 555 U.S. 555, 569 (2009) (internal quotation marks omitted). This "rule accounts for the fact that risk

information accumulates over time and that the same data may take on a different meaning in light of subsequent developments . . . ." *Id.* Still, the new analysis must reveal "risks of a different type or of greater severity or frequency" to constitute "newly acquired information." *Id.* (internal citation and quotation marks omitted).

B.

The Knights claim Boehringer's post-approval study of the RE-LY data provided "newly acquired information" about the risks Pradaxa posed to certain patients and the need for blood monitoring. To assess this argument, we will first consider the final paper by Dr. Reilly and then the internal discussions at Boehringer and the preliminary drafts of the paper.

1.

For several reasons, the published Reilly Paper, which was the culmination of the RE-LY post-approval analysis, does not offer "newly acquired information." First, the finalized version of the Reilly Paper was not sent to the publisher until June 2013, after Knight's bleed. Thus, by the date the paper was published, the information in it would not have made any difference to Knight.

Second, and more substantively, although the paper consists of a "new analysis of previously submitted data," it does not "reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." 21 C.F.R. § 314.3(b). To be sure, the paper discusses the correlation between Pradaxa blood concentration levels and bleeding risk. But the FDA was already aware of this correlation. In the FDA's own analysis when it approved Pradaxa, it concluded "[t]here is a significant relationship

between [Pradaxa] exposures and incidence of bleeding events," and "the probability of a life-threatening bleed within 1 year in a typical patient is predicted to increase from 0.27% to 1.82%" depending on Pradaxa blood concentration levels. J.A. 1172. "Given that the FDA already knew of the association between high Pradaxa blood plasma concentrations and bleeds (and nonetheless did not require the defendants specifically to warn of it in the label), the Reilly Paper's reference to that association does not constitute . . . newly acquired information." *Roberto v. Boehringer Ingelheim Pharm., Inc.*, No. CPL-HHD cv16-6068484S, 2019 WL 5068452 (Conn. Super. Ct. Sept. 11, 2019) (discussing the same paper in a similar claim).

Moreover, the physician label in place since November 2011, and even before, warned of these risks. The original label, from October 2010, instructed to "[r]educe the dose of PRADAXA in patients with severe renal impairment" because those patients' poor kidney function would result in higher blood concentrations of the drug. J.A. 1256. And the November 2011 label explained that "P-gp inhibition and impaired renal function are the major independent factors that result in increased" Pradaxa blood concentration levels. J.A. 1283. Therefore, it advised that "[r]enal function should be assessed . . . prior to initiation of treatment with PRADAXA." J.A. 1282.

Third, the paper's conclusion—that "[t]here is no single plasma concentration range that provides optimal benefit-risk for all patients"—plainly does not establish any new risk. J.A. 113. That conclusion tracked Boehringer's warnings since the FDA's initial approval of Pradaxa and its labeling. Therefore, the article cannot constitute "newly acquired

information" because it did not "reveal risks of a different type or greater severity or frequency . . . ." 21 C.F.R. § 314.3(b).

2.

The more difficult question is whether the preliminary conclusions that emerged before the analysis was complete, and which differed from the ultimate conclusion in the Reilly Paper, constitute "newly acquired information." Recall that in August 2011, just two months before Knight was first prescribed Pradaxa, Dr. Reilly e-mailed an internal executive "that the conclusions that appear to emerge from this paper are not the ones currently wished for by marketing (that dose adjustment will optimize therapy) . . . ." J.A. 510. Indeed, a few months later, Dr. Reilly circulated a draft paper which concluded that there was a range of Pradaxa blood concentration levels which optimized the "balance between benefit and risk" and that up to twenty percent of patients could fall outside that optimal range. J.A. 927.

Despite this evidence, the record does not demonstrate that Dr. Reilly's emails or the draft paper's preliminary assessments of an optimal Pradaxa blood concentration level reflected a revelation of risks of a different type or greater severity or frequency. Although Dr. Reilly initially thought the analysis might reveal an optimal blood concentration range, his view was preliminary, as evidenced by his comment that he wanted to "see where this paper ends up." J.A. 510. And after circulating a draft version that concluded such a range existed, Boehringer continued to analyze the data and work on the paper. Almost two years later, Boehringer came to a different conclusion.

Importantly, the scientific and regulatory community accepted Boehringer's final conclusion. The final version of the paper was published, peer-reviewed and submitted to the FDA. And, after reviewing the Reilly Paper, the FDA has continued to approve labels with no monitoring requirement. This undermines the Knights' claim that Boehringer's preliminary analysis made it immediately apparent, before the paper was published, that an optimal blood concentration range existed. Because the new analysis did not "reveal" the conclusion that an optimal blood concentration range existed, Dr. Reilly's preliminary thoughts and draft conclusions were not "newly acquired information." 21 C.F.R. § 314.3(b).[9]

Our decision today, however, should not be construed to require final, peer-reviewed publication of an analysis to constitute newly acquired information. Some findings may be revealed instantly. Indeed, that occurred on some of the issues here. Boehringer made a CBE label change before Dr. Reilly even circulated the draft paper to clarify that "[p]atients with severe renal impairment were not studied in RE-LY" and "P-gp inhibition and impaired renal function are the major independent factors that result in increased" Pradaxa blood concentration. J.A. 1284. Boehringer's analysis reasonably justified these label changes because it immediately and conclusively demonstrated a

[9] Several courts that have considered this identical question have reached the same result. These courts, despite the lack of precedential guidance, have all concluded that the preliminary discussions and conclusions that emerged from the RE-LY study regarding blood monitoring were not "newly acquired information." *See Silverstein v. Boehringer Ingelheim Pharm., Inc.*, 9:19-cv-81188-RAR, 2020 WL 6110909 *33–36 (S.D. Fla. Oct. 7, 2020); *Lyons v. Boehringer Ingelheim Pharm., Inc.*, No. 1:18-cv-04624-WMR, 2020 WL 5835125 *8–9 (N.D. Ga. Sept. 29, 2020); *Roberto*, 2019 WL 5068452 at *16. We commend their thorough analyses of this issue and echo their conclusions.

strong relationship between kidney function and Pradaxa blood concentration levels. But the fact that some findings in an analysis may be revealed instantly does not mean that all are. In contrast to the risks added to the physician label, monitoring Pradaxa blood concentration levels needed further study to "see where this paper ends up." J.A. 510. Based on the record submitted to us, neither Dr. Reilly nor Boehringer had come to any conclusion on this issue.

Likewise, peer review and publication of an article do not themselves prevent any contrary findings from qualifying as newly acquired information. If, for example, the record revealed that the company reached a conclusion about risks of a different type or risks of greater severity or frequency, but either elected not to publish or published something different in bad faith, the unpublished conclusion might indeed qualify as newly acquired information. That appears to be the Knights' position here. But the record does not indicate that Boehringer's scientists reached a conclusion on an optimal blood concentration range, or that the final, published results were reached in bad faith.[10]

Finally, we caution against a quick trigger in determining the existence of newly acquired information. It is imperative for the scientific process that open dialogue and

[10] Likewise, the other documents the Knights cite do not establish that Boehringer had "newly acquired information." The 2011 Clinical Overview Statement discusses that the European label will refer to 200 ng/mL to be associated with an increased risk of bleeding. But even if this were considered "data, analys[is], or other information" within the meaning of the CBE regulation, the FDA was already aware of the association between high blood plasma concentrations of Pradaxa and the increased risk of bleeding. In fact, the FDA Clinical Pharmacology Review includes a graph depicting this association. So, any "information" here could not have been "newly acquired" because the FDA already knew about it. For the same reason, the Company Core Data Sheet was not "newly acquired information." In fact, it was submitted to the FDA before it approved Pradaxa.

exchange of ideas take place during an analysis and drafting of a paper. That, along with airing and testing opposing opinions, results in better decisions. That is why hypotheses, differing viewpoints and even preliminary conclusions are not "reliable evidence of new risks." *Roberto*, 2019 WL 5068452 at *16. If they were, companies might discourage the open dialogue needed to reach the best results. Or, unnecessary warnings might flood labels and distract from real risks. Accordingly, preliminary thoughts and discussions are not "reasonable evidence of a causal association with a drug" and cannot, without more, reveal "newly acquired information." 21 C.F.R. § 201.57(c)(6)(i).

In sum, there is no bright-line, one-size-fits-all line marking the moment when an analysis reveals new information. A careful review of the record is needed to determine whether a conclusion has been reached. Such a review here reveals that Boehringer did not have "newly acquired information" regarding an optimal Pradaxa blood concentration level which would have warranted a unilateral change to the physician label. As a result, the state-law fraud claim is preempted.

III.

For the reasons set forth above, the judgment below is

REVERSED.