IN THE UNITED STATES DISTRICT COURT FOR THE WESTERN DISTRICT OF MISSOURI WESTERN DIVISION

Max Ridings and Sue Ridings,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	**Civil Action Number**
	)	**15-00020-CV-W-JTM**
Scott Maurice, *et al.*,	)	
	)	
Defendants.	)	

ORDER ON PRELIMINARY LEGAL QUESTION OF FEDERAL PREEMPTION

A. Litigation overview

On December 11, 2014, plaintiff Max Ridings ("Ridings") and his wife initiated this product liability litigation by filing a petition in the Circuit Court of Jackson County, Missouri, alleging injuries arising from Ridings' use of the prescription drug Pradaxa as prescribed to him by his physician, Dr. Sanjaya Gupta ("Dr. Gupta"). Ridings' lawsuit asserted various theories of liability under Missouri tort law including strict liability, negligence, breach of implied and express warranty, violation of the Missouri Merchandising Practices Act, fraud, and negligent misrepresentation.[1] In this lawsuit, the Ridings named two categories of defendants, to wit:

(1) the corporate entities that allegedly manufactured and distributed Pradaxa in the United States – Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim Corp., Boehringer Ingelheim USA Corp., Boehringer Ingelheim Pharma GMBH & Co. KG, and Boehringer Ingelheim International GMBH (collectively referenced herein as "Boehringer"); and

[1] As a derivative of Ridings' claims for damages, his wife and co-plaintiff, Sue Ridings, asserted claims for loss of consortium.

(2) five individual sales representatives of Boehringer Ingelheim Pharmaceuticals, Inc. – Scott Maurice, Matthew Hoesch, Maurice Jackson, John Mimnaugh, and Jennifer Caskey.[2]

On January 9, 2015, Boehringer removed the case to this Court based on diversity of citizenship. To that end, there was no dispute that Ridings and his wife were citizens and residents of the State of Missouri and the Boehringer entities were citizens of various jurisdictions, but were not citizens of Missouri. However, it was also evident that four of the five named individual sales representatives were citizens of Missouri.[3] With respect to the Missouri sales representatives, though, Boehringer's removal papers included declarations from the individuals that each detailed that they:

(a) played no role in the design, testing or manufacture of Pradaxa,

(b) played no role in the development or publishing of Pradaxa package inserts or marketing materials accompanying the drug or otherwise disseminated to health care providers,

(c) did not create, alter, revise or have any involvement in obtaining any approval for any warnings or instructions relating to Pradaxa,

(d) did not personally know and have not had any direct dealings or communications with the Ridings,

(e) did not personally know or ever have any Pradaxa-related contact with Dr. Sanjaya Gupta; and

(f) did not sell Pradaxa or make any warranties or representations regarding Pradaxa to the Ridings or Dr. Sanjaya Gupta.

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[2] Ridings initially also asserted claims against John Does 1-20 described as unknown "individuals, partnerships, or corporations who are or were engaged in the business of marketing, selling, distributing, and promoting Pradaxa."

[3] Scott Maurice appeared to be a citizen of the State of Kansas. Further, the fictitious John Doe defendants were "disregarded" for purposes of citizenship and diversity considerations. 28 U.S.C. § 1441(b)(2).

Arguing that the individual sales representatives were fraudulently joined, Boehringer asserted that there was complete diversity between the plaintiffs and properly named defendants and, in light of the fact that the amount in controversy exceeded $75,000, jurisdiction was proper in this Court pursuant to 28 U.S.C. § 1332. On January 26, 2015, Ridings timely filed a motion to remand the case back to state court [Doc. 13].

On March 31, 2015, this Court entered an order [Doc. 21] generally finding that Boehringer had sufficiently established that there was no arguably "reasonable basis for predicting that [Missouri] law might impose liability [on the allegedly fraudulently joined defendants] based upon the facts involved." *Block v. Toyota Motor Corp.*, 665 F.3d 944, 947 (8th Cir. 2011). Consequently, the Court ruled:

> The Court is cognizant of the fact that the Ridings did not choose a federal forum for their case. However, Congress has explicitly enacted a removal statute that itself expressly takes into account the doctrine of fraudulent joinder. While a plaintiff's choice of forum is entitled to great deference, at the same time, this Court is obligated to exercise federal jurisdiction over cases that are properly brought before it. This is just such a case. The motion to remand is denied.

[Doc. 21]. The Court subsequently dismissed without prejudice the individual sales representatives as party-defendants pursuant to FED. R. CIV. P. 12(b)(6).

After the Court entered its order, the Judicial Panel on Multidistrict Litigation transferred the case to the United States District Court for the Southern District of Illinois where the MDL Panel had established centralized proceedings for all Pradaxa federal cases filed in district courts nationwide, centralizing the litigation before the Honorable David Herndon. After the case was transferred to the Southern District of Illinois, Boehringer reached a settlement of several thousand Pradaxa MDL cases. However, Ridings' litigation was not included in the "global" settlement. Consequently, on May 16, 2016, the case was transferred back to this Court.

After the case was returned to this Court, the case was set for trial on April 29, 2019, and the parties engaged in a period of extensive pretrial discovery. At the conclusion of discovery, Boehringer filed a substantial motion for summary judgment [Doc. 89] based primarily on the assertion that all of Ridings' state law product liability claims were preempted under the Supremacy Clause of the United States Constitution. U.S. CONST. art. VI, cl. 2.

In considering Boehringer's motion, the Court noted that Ridings' claims could be generally categorized as assertions that:

(1) Pradaxa was defectively designed, and

(2) Boehringer failed to warn.

With regard to the former category of claims, the Court issued an order finding that the summary judgment record was sufficient to establish as a matter of law that Ridings' design defect contentions were preempted.

> This Court likewise concludes that Ridings' claims herein of a design defect, insofar as they are premised on the failure of Boehringer to develop, seek and obtain approval for and/or market a reversal agent for Pradaxa sooner that it did are preempted. As the Eighth Circuit has noted, when confronted with such an argument for the impossibility of complying with both federal drug laws and state tort laws, a plaintiff must be able to explain how Boehringer "could avoid liability under Missouri law for the alleged design defects without changing its product, changing its labeling, or leaving the market." *Brinkley v. Pfizer, Inc.*, 772 F.3d 1133, 1141 (8th Cir. 2014). In the absence of such an explanation, Ridings' "design defect claims – whether sounding in strict liability or negligence – are preempted by impossibility." *Id*.

[Doc. 124].

With regard to the failure-to-warn allegations, however, the Court found that the summary judgment record did not establish sufficient material facts, about which there were no

genuine issues, to support concluding as a matter of law that the failure-to-warn claims were preempted.

> Based on the record before the Court, a blanket ruling summary judgment finding federal preemption cannot be granted on the failure-to-warn claims. Certainly, if Ridings argues that Pradaxa's warnings were defective or negligently worded and Ridings asserts that the Pradaxa label should have included a warning in a form substantially similar to the form rejected or modified by the FDA, there would be clear evidence as a matter of law and the Court would be inclined to disallow such assertions in front of the jury. However, it is evident that the issues will not be so clear cut so as to rule on the issue as a matter of law. There will be factual disputes as to the equivalency of the warnings advocated by Ridings and the status of "newly acquired information" available to Boehringer at various times after the FFA approved Pradaxa. . . . In this case, the Court does not find summary judgment appropriate on the record. At trial, Ridings will be permitted to offer evidence of alternate warnings for Pradaxa if he makes a foundational showing that "newly acquired information" existed such that Boehringer could have unilaterally changed its label in accordance with the CBE regulation. In response, Boehringer may offer evidence that it could not have changed the label, by the CBE process or otherwise, or if it could, there is clear evidence the FDA would have rejected the changed label.

Doc. 124 (*emphasis added*). At that point, the case was scheduled to proceed to a jury trial commencing on October 28, 2019.

At around the same time that the Court was ruling on Boehringer's motion for summary judgment, the United States Supreme Court issued its decision in another pharmaceutical product liability case, *Merck Sharp & Dohme v. Albrecht*, 139 S. Ct. 1668 (2019). With regard to the procedural handling of federal preemption litigation, the *Albrecht* court found:

> We turn now to what is the determinative question before us: Is the question of [federal preemption in a failure-to-warn case involving a regulated pharmaceutical] primarily one of fact, normally for juries to decide, or is it a question of law, normally for a judge to decide without a jury? [W]e answer this question by concluding that the question is a legal one for the judge, not a jury.

Albrecht, 139 S. Ct. at 1679.

Consistent with *Albrecht*, the Court concluded that it – and not a jury – would need to be the factfinder[4] on the potentially dispositive question of whether Boehringer's affirmative defense of preemption could be established so as to bar Ridings' state law failure-to-warn claims. As a consequence, the Court ultimately concluded that the interests of judicial resources and efficiency would be best served by cancelling the jury trial scheduled for October 28, 2019, and proceed instead with a hearing to the Court focused solely on the issue of whether Ridings' state law failure-to-warn claims were preempted.

In advance of the hearing, the Court explained that, regardless of the failure-to-warn theories that Ridings may pursue, the essential inquiry was whether Boehringer could have given a different warning. To keep the hearing focused on the actual issue in the case, the Court thus required Ridings to specifically identify the warning (or warnings) that he believed should have

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[4] In *Albrecht*, the Court acknowledged that the determination of preemption will often require the Court to make factual determinations based on competing and contradictory evidence.

> We understand that sometimes contested brute facts will prove relevant to a court's legal determination about the meaning and effect of an agency decision. For example, if the FDA rejected a drug manufacturer's supplemental application to change a drug label on the ground that the information supporting the application was insufficient to warrant a labeling change, the meaning and scope of that decision might depend on what information the FDA had before it. Yet in litigation between a drug consumer and a drug manufacturer (which will ordinarily lack an official administrative record for an FDA decision), the litigants may dispute whether the drug manufacturer submitted all material information to the FDA. [I]n those contexts where we have determined that the question is "for the judge and not the jury," we have also held that "courts may have to resolve subsidiary factual disputes" that are part and parcel of the broader legal question.

Albrecht, 139 S. Ct. at 1680.

been given by Boehringer. Given such proposed warnings, the Court thereafter wanted the parties to focus on the resulting central issues, to wit:

(1) Is there evidence sufficient to conclude that Boehringer could and should have availed itself of the applicable federal regulations and given the warning(s) advocated by Ridings; and

(2) If so, is there nonetheless "clear evidence" that the FDA – even if presented with such evidence – nonetheless would have rejected the warning(s) advocated by Ridings.

In addition to this legal framework, the Court noted that preemption is an affirmative defense and as such, typically, the burden of proof rested with the party asserting the affirmative defense. On the other hand, the Court observed that it was not the usual practice to ask a party to prove a negative (*e.g.*, asking a pharmaceutical company to prove that there was no new evidence available). For purposes of the preemption hearing, the Court concluded that the best practice was to view the question of preemption in drug litigation as involving a shifting burden:

(1) initially, a defendant must make an initial *prima facie* showing of preemption for the warning it did provide with its drug,

(2) if that showing is made, a plaintiff then bears the burden of coming forward with evidence sufficient to conclude that the defendant could and should have availed itself of the applicable federal regulations and given a different warning(s) advocated by the plaintiff, and

(3) if that showing is made, the defendant then bears the burden of coming forward with "clear evidence" that the FDA – even if presented with such "new" evidence – nonetheless would have rejected the warning(s) advocated by the plaintiff.

In this case, there was no dispute that the warning label for Pradaxa in effect at the time Ridings was using the drug had been approved by the FDA and, as a consequence, in general, Boehringer was barred from changing that label. In the Court's view, then, even prior to the hearing, there

was a sufficient showing to advance to the second stage of the preemption analysis. Consequently, Ridings – as the party with the second-step burden – would present evidence first.

On October, 28-31, 2019, the Court conducted a hearing on the federal preemption issue. Ridings and his wife appeared in person and through their counsel Kenneth McClain, Daniel Thomas, and Timothy Kingsbury, all with Humphrey, Farrington & McClain, P.C. Boehringer appeared through counsel Shankar Duraiswamy and Paul Schmidt with Covington & Burling LLP, Eric Hudson with Butler Snow O'Mara Stevens, & Cannada PLLC, and Perry Brandt with Bryan Cave Leighton Paisner, LLP. Numerous exhibits and deposition testimony were offered by the parties and two witnesses testified in person: Laura Massey Plunkett for Ridings and Maureen Oakes for Boehringer. Following the hearing, a transcript was prepared, and the parties submitted their respective proposed findings of fact and conclusions of law.

Following a bench hearing – particularly when the hearing addresses such a complex and potentially dispositive matter as federal preemption – the Court believes adherence to the standards associated with bench trials is appropriate. To that end, following a bench trial, a "court must find the facts specially and state its conclusions of law separately . . . in an opinion or a memorandum of decision filed by the court." FED. R. CIV. P. 52(a). However, in such an opinion or memorandum, a court "need not make specific findings on all facts and evidentiary matters brought before it, but need find only the ultimate facts necessary to reach a decision in the case." *United States for Use of R. W. Vaught Co. v. F. D. Rich Co.*, 439 F.2d 895, 899 (8th Cir. 1971). In addition, a court's findings of fact and conclusions of law "are adequate if they afford a reviewing court a clear understanding of the basis of the trial court's decision." *Collins v. Henderson*, 180 F.3d 988, 990 (8th Cir. 1999).

Based on consideration of the evidence adduced, whether or not explicitly discussed herein, the Court makes the following findings of fact and conclusions of law:[5]

B. Findings of Fact

1. Overview

In February of 2012, Ridings was seen by his cardiologist, Dr. Gupta, presenting to the doctor with a previously diagnosed condition known as atrial fibrillation ("AF").

> [AF is] a problem with the electrical system of the heart that causes an irregular heart rhythm. Atrial fibrillation can produce palpitations, shortness of breath, lightheadedness, weakness, and chest pain, or may occur without symptoms. The main concern, however, is that atrial fibrillation can lead to the formation of blood clots in the heart, which can travel to the brain and cause a stroke.

Ellis F. Unger, M.D., *Atrial fibrillation and new oral anticoagulant drugs*, U.S. FOOD AND DRUG ADMIN., NEWS & EVENTS FOR HUMAN DRUGS (Oct. 16, 2015) [www.fda.gov/drugs/news-events-human-drugs/atrial-fibrillation-and-new-oral-anticoagulant-drugs] ("Unger"). AF may increase a person's risk of developing a stroke by five times. While there are drug regimens and medical procedures that can be attempted "to correct the fundamental heart rhythm problem . . . the main focus of treatment is to try to decrease the rate of stroke by preventing the formation of these blood clots [by prescribing anticoagulant drugs or 'blood thinners']." Unger.

[5] To the extent any findings of fact have been "designated in error as conclusions of law [they should] be deemed findings of fact and any conclusions of law designated in error as findings of fact shall be deemed conclusions of law.'" *In re Cameron*, 219 B.R. 531, 534 (Bankr. W.D. Mo. 1998). *See also* 9C CHARLES A. WRIGHT & ARTHUR MILLER, FEDERAL PRACTICE & PROCEDURE § 2579 (3d ed. 1998 & 2019 Supp.) (appellate courts "will regard a finding or conclusion for what it is, regardless of the label the trial court may have put on it").

For most of the sixty years prior to 2012, Warfarin (marketed under the brand name Coumadin) had been the only drug approved in the United States for the prevention of stroke in patients with AF. Unger. On October 19, 2010, however, the FDA approved the drug dabigatran to reduce the risk of stroke and systemic embolism in patients with non-valvular AF. In the United States, dabigatran was manufactured and distributed under the name Pradaxa.

In addition to approving a drug for marketing and usage in the United States, the FDA also must approve all labeling submitted by pharmaceutical companies for their approved drugs. A proposed label must be supported by reliable scientific data and, broadly speaking, cannot contain mere hypotheses or interim finings and discussions. If the FDA rejects proposed labeling language, a pharmaceutical company may not include the rejected language and/or information and/or warnings in the drug's label.

2. The initial FDA approval of Pradaxa in 2010

Because Pradaxa acts as a blood thinner, Boehringer, the FDA and health professionals have examined and considered its potential for causing adverse health consequences – including the risk of major bleeding events and hemorrhagic strokes in patients taking the drug.[6]

> Anticoagulants . . . produce a striking (more than 50%) decrease in the rate of stroke, but they also prevent clotting in locations and situations where clotting is desirable. In other words, they can cause bleeding.

Unger. Prior to Pradaxa's approval, the FDA considered a study funded by Boehringer, the Randomized Evaluation of Long-Term Anticoagulation Therapy ("RE-LY"), that involved a randomized trial designed to compare two fixed doses of dabigatran, each administered in a blind manner, in patients who had atrial fibrillation and were at increased risk for stroke.

[6] For instance, one of the known concerns associated with Coumadin was an increased risk of hemorrhaging in patients with atrial fibrillation.

a. Pre-FDA-approval consideration of plasma concentration monitoring

Based on its analysis of the RE-LY data, the FDA concluded that a marginal, but statistically significant, "relationship between dabigatran trough concentration[7] and [the] probability of ischemic stroke has been established." With regard to bleeding, the FDA's analysis of the submitted data also found "[t]he probability of a life-threatening bleed . . . increases with increasing dabigatran concentration."

The RE-LY data submitted to the FDA by Boehringer also reflected that plasma concentration[8] data had been collected in a sub-set of test patients. The RE-LY data reflected that "the slope of the [stroke] curve decreases with increasing dabigatran plasma concentrations" and that "[t]here is relatively little difference in stroke risk across a wide range of higher dabigatran trough[9] concentrations." By contrast, "[t]here was a strong relationship between trough dabigatran concentration and an increased probability of having a major bleed" across all concentrations.

Prior to Pradaxa's initial approval, the FDA studied Boehringer's exposure-response analyses and, using the RE-LY data submitted by Boehringer, conducted an "independent"

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[7] In medicine, a trough level or trough concentration is the lowest concentration reached by a drug before the next dose is administered. The measurement is often used in therapeutic drug monitoring. Typically, with the passage of time, drug molecules are metabolized or otherwise cleared by the body, so that the concentration of drug that remains available to a patient drops. In medications that are administered periodically, the trough level is measured just before the administration of the next dose in order to avoid overdosing.

[8] A drug's efficiency may be affected by the degree to which it binds to proteins (plasma) within the blood. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse. Alternatively, the more a drug binds, the higher the dosage that may be necessary to deliver efficacy.

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analysis of the relationship between Pradaxa plasma concentrations in patients and the probability of strokes and major bleeds. The FDA ultimately concluded that "[a] relationship between dabigatran trough concentration and probability of ischemic stroke has been established." With regard to major bleeding, the FDA's analysis showed that "[t]he probability of a life-threatening bleed . . . increases with increasing dabigatran concentration."

The FDA ultimately presented the results of its independent exposure-response analyses at its September 20, 2010 Advisory Committee meeting. In the presentation, the FDA concluded that "[h]igher dabigatran concentrations result in lower probability of ischemic stroke" and "higher probability of life-threatening bleed." Consequently, the FDA reasoned that the desirability of higher Pradaxa plasma concentrations – and thus higher dosages of Pradaxa – depended on whether it was preferable to avoid strokes (statistically less likely with higher plasma concentrations) or avoid major bleeds (statistically more likely with higher plasma concentrations). Considering the alternatives, the FDA found that "the irreversible effects of strokes and systemic emboli have greater clinical significance than nonfatal bleeding." In practical terms, the FDA thus approved a 150 mg dose[10] of Pradaxa (likely to lead to higher plasma levels and, thus, a higher risk of bleeding but a lower risk of stroke) but did not approve a 110 mg dose of Pradaxa (more likely to lead to lower plasma concentrations and, thus, a lower risk of bleeding but a higher risk of stroke).[11]

On September 27, 2010, Boehringer sent the FDA its proposed labeling for Pradaxa. The proposed label contained recommendations regarding use of the 110 mg dose of Pradaxa in

[10] Because of its emphasis on preventing strokes, the FDA considered, but never approved, a dose of Pradaxa even higher than 150 mg.

[11] The FDA further found that it did not "see a need for [therapeutic] monitoring [of plasma] concentration" in individual patients.

certain patient populations. Boehringer also proposed to inform physicians in its label that "the aPTT test[12] may be useful to assist in determining an excess of anticoagulant activity" and "[a]n aPTT greater than 80 sec is associated with a higher risk of bleeding."

Notwithstanding Boehringer's proposed label, when the FDA approved Pradaxa for the American market on October 19, 2010, the FDA did not approve a 110 mg dose of Pradaxa and the FDA-approved "launch label" for the 150 mg dose of Pradaxa did not contain any specific recommendation to monitor plasma concentrations or to utilize any specific aPTT test measurement, although the Pradaxa "launch label" did instruct that "[b]leeding risk can be assessed by the ecarin clotting time[13] (ECT) [and if ECT is not available, the aPTT test provides an approximation of PRADAXA's anticoagulant activity]" and that "[m]easurement of aPTT or ECT may help guide therapy."

Several times after October 19, 2010 and prior to July 31, 2013,[14] the FDA approved the labeling for Pradaxa. None of the FDA-approved labels recommended plasma monitoring. For instance, in January 2012, the FDA approved Pradaxa labeling and indicated that, "[g]enerally, the extent of anticoagulation does not need to be assessed." Similarly, in December of 2011, the FDA issued a Drug Safety Communications[15] recommending that prescribers follow Pradaxa's

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[12] An "activated partial thromboplastin time" is a blood test that characterizes coagulation of the blood. Boehringer informed the FDA that it had advised the FDA that the aPTT test was a widely-available laboratory test that "close[ly] correlat[ed]" with Pradaxa plasma concentrations and, specifically, an aPTT test "seemed sufficient to detect excessive anticoagulation with dabigatran." In response to the FDA's request for additional information, Boehringer informed the FDA that an aPTT between 75 and 85 seconds "would be appropriate cut-off points."

[13] ECT is "highly correlated with dabigatran concentrations," but unlike the aPTT test, it is "not widely available in hospital laboratories" in the United States.

[14] As discussed in more detail *infra,* the date that Ridings was hospitalized.

[15] A publicly available document that provides the FDA's opinion on a safety topic.

label, noting that the agency "continues to believe that Pradaxa provides an important health benefit when used as directed and recommends that healthcare professionals who prescribe Pradaxa follow the recommendations in the approved drug label."

b. Pre-FDA-approval consideration of Pradaxa interactions with P-gp inhibitors

Prior to approval of Pradaxa, Boehringer performed a series of "drug interaction studies" that revealed that plasma concentrations of Pradaxa and bleeding risk may increase when Pradaxa is taken concomitantly with a P-gp inhibitor.[16] Boehringer shared those conclusions, along with the underlying study data, with the FDA prior to Pradaxa's approval. Accordingly, as part of its review of the Pradaxa NDA, the FDA analyzed Pradaxa's potential interaction with P-gp inhibitor medications, ultimately concluding that despite "an interaction liability of dabigatran and . . . P-gp inhibitors," "[n]o dose adjustment is required." In 2012, Boehringer twice sought to warn that P-gp inhibitor co-medication with Pradaxa increased a risk of bleeding, but the FDA rejected Boehringer's proposals, stating that P-gp inhibition is an "independent risk factor[] for bleeding that do[es] not need to be called specifically in the label."

c. Pre-FDA-approval consideration of the use of Pradaxa in patients with GERD

The RE-LY data provided to the FDA by Boehringer prior to the approval of Pradaxa showed that use of an anticoagulant in patients with "gastritis-like symptoms," including GERD,[17] were associated with an increased risk of a "major" GI bleed by 3-to-4-fold and "any"

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[16] P-gp or P-glycoprotein 1 is an important protein of the human cell membrane that pumps many foreign substances out of cells. P-gp can reduce the efficacy of some drugs. Certain foods and many drugs inhibit P-gp. Most drugs that act as a P-gp inhibitor do so incidentally and not as their main intended mechanism of action.

[17] Gastroesophageal reflux disease, or acid reflux. GERD is a condition where stomach acid flows back into the esophagus (the tube connecting the mouth and stomach).

GI bleed by 2-to-3-fold. As a consequence of the data provided to it and (presumably) its own independent investigation, the FDA label for Pradaxa warns that patients on Pradaxa have "an increased incidence of gastrointestinal adverse reactions[,] . . . including GERD," relative to warfarin patients. Further, physicians are directed to counsel their patients to inform the physician if the patient experiences any "signs or symptoms" of various conditions, including GERD. Since the introduction of Pradaxa to the American market, the FDA has never directed Boehringer to warn physicians about the "measurable" risks found in the RE-LY data, beyond the GERD warnings that already appear in the Pradaxa label.

3. Post 2010 occurrences[18]

a. The 2011 Euro Label

On April 1, 2011, the European Medical Agency ("EMA) authorized the use of Pradaxa in the EU. The EMA had been provided with substantially similar, if not identical, information regarding Pradaxa by Boehringer. The resulting European Summary of Product Characteristics ("Euro Label") for Pradaxa is different from the Pradaxa labeling approved by the FDA in several respects. For instance, the Euro Label states:

> Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.

The Euro Label further provides information on how to use measurements of plasma concentrations to avoid excessively high exposure. Specifically, the Euro Label informs

[18] Various post FDA-approval matters were referred to or referenced in the evidence as being (or not being) adequate newly discovered evidence regarding Pradaxa. The Court does not address every such matter. To the extent that such matters are not specifically discussed in this order, the Court has concluded that the matter is duplicative of other matters specifically discussed herein or fails to raise even a colorable claim to be newly discovered evidence under the relevant standards.

prescribers of available tests – diluted thrombin time (dTT), ECT, and aPTT – and provides guidance in the form of actual coagulation test thresholds. As previously noted, Boehringer provided data to the FDA regarding its analyses *viz-a-viz* the aPTT test. With respect to the other two tests, Boehringer informed the FDA

> There are other more specific tests like Ecarin clotting time and thrombin time, which are quite specific and sensitive and have a linear relationship. However, they're not that widely available and their methodologies can vary.

In September of 2012, Boehringer submitted to the FDA the more-detailed EMA-approved label for Pradaxa. The FDA directed no change to the Pradaxa label based on the submission of the Euro Label.

b. Boehringer's July 15, 2011 Clinical Overview Statement

On July 15, 2011, Boehringer issued a Clinical Overview Statement ("the 2011 COS"). The document was prepared as a "reference document" for the Pradaxa Prescriber Guide, a EMA publication that recommended use of the 110 mg dose of Pradaxa "[w]hen excessive dabigatran exposure is identified in patients at high risk of bleed" and informed physicians of thresholds for various coagulation tests (aPTT, ECT, and dTT) that could be utilized to "identify" patients with "excessive dabigatran exposure." As previously noted, in 2010, the FDA had rejected Boehringer's request to market a 110 mg dose of Pradaxa in the United States.

The 2011 COS again looked at the RE-LY clinical trial data that identified values with the dTT and ECT tests used to identify bleed risk in patients. With respect to the dTT test, the 2011 COS noted:

> Based on clotting times determined by the [dTT test] at concentrations of 215 ng/mL . . ., a diluted thrombin clotting time of >65 sec at trough is considered to represent a conservatively assessed cut-off value**.**

The dTT test (also referred to as a Hemoclot test) is not approved in the United States. The 2011 COS also provided the information related to the ECT test:

> The 90th percentile of trough ECT after 150 mg BID as observed in RE-LY was 103 and therefore, exceeding a 3-4-fold elevated level compared to baseline will likely be associated with a higher risk of bleeding.

The information is substantially similar to the information provided to the FDA prior to its approval of Pradaxa. At that time, Boehringer noted to the FDA that an analysis of the RE-LY data showed that "the risk of 93.0 ng/mL to 7.5% and hence be almost doubled at 215 ng/mL, the 90th percentile of measured trough concentrations." And Boehringer, more broadly, also informed the FDA that "aPTTs above 80 sec were associated with a higher major bleed rate" and an "ECT [test] displayed a linear relationship with dabigatran standard concentrations."

c. Boehringer's 2012 computer simulation findings

In 2012, Boehringer performed a series of modeling exercises to explore whether exposure measurement might further improve Pradaxa's "positive benefit-risk balance." The modeling was done through a complex computer simulation using RE-LY data. Boehringer's initial analyses suggested that dose-titration based on plasma concentrations "could preserve the effect on ischemic stroke prevention but with a reduction of major bleeding events compared to well controlled [Coumadin] of perhaps up to 30-40%." Based on these promising preliminary results, Boehringer on June 25, 2012 sought to patent its dose-titration method.

However, following further analysis, Boehringer concluded that "the scientific data would not support such a concept," because when Boehringer "compared what the modeling and simulation data would [predict] compared to what [Boehringer] actually saw in RE-LY," the actual observed data in RE-LY were "quite different" from what the computer modeling suggested. In light of the discrepancies, Boehringer withdrew its patent application before any

rights were granted. While it does not appear that Boehringer ever shared its dose-titration computer modeling findings with the FDA, Boehringer did provide a detailed explanation and analysis of the simulations to the EMA. The EMA "endorsed" Boehringer's conclusion that the computer simulations had "limitations" that rendered them unable to predict actual patient outcomes.

d. The 2013 Reilly paper

Following the introduction of Pradaxa into the American market, Boehringer continued analyzing the relationship between plasma concentrations and stroke and bleed risk based on the RE-LY data. As a result of this analysis, in July of 2013, the JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY accepted an article written by Dr. Paul Reilly and other scientists ("the Reilly paper"). The Reilly paper – published in February of 2014[19] – examined the effect of plasma concentrations on stroke and bleed risk and reached conclusions consistent with the FDA's pre-approval exposure-response analyses of the RE-LY data. Similar to the FDA in initially approving Pradaxa and the "launch label," the authors of the Reilly paper reached a consensus that "[t]here is no single plasma concentration range that provides optimal benefit–risk for all patients."

In May of 2014, Boehringer submitted a Periodic Safety Update Report ("PSUR") to the FDA. As part of that PSUR, Boehringer submitted the Reilly paper to the FDA. The FDA has never exercised its legal powers to direct a label change for Pradaxa based on the Reilly pape

[19] Paul A. Reilly, PhD, *et al.*, "The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)", J. AMER. COLL. CARDIO. 2014; 63:321-28.

e. The 2014 BRITISH MEDICAL JOURNAL articles

On July 23, 2014, the BRITISH MEDICAL JOURNAL published several articles[20] (collectively referenced herein as "the Cohen articles") that set out to show that Boehringer had "withheld from [governmental drug] regulators important analyses regarding how to use [Dabigatran] as safely and effectively as possible." The Cohen articles reported that a 2011 draft of the Reilly paper had "suggested there was an optimal plasma concentration range." The Cohen articles also excerpted and summarized various e-mails authored by Boehringer scientists and independent scientists discussing drafts of the Reilly paper and the possibility of a therapeutic range. The Cohen articles further quoted from the interim results of the dose-titration modeling Boehringer had performed.

The day after publication of the particular issue of the BRITISH MEDICAL JOURNAL, Boehringer transmitted the Cohen articles to the FDA and EMA. Based on the Cohen articles, EMA asked Boehringer a series of questions. Boehringer submitted to the FDA the questions posed by the EMA as well as Boehringer's responses. Those responses provided the FDA with extensive information about Boehringer's computer modeling efforts, including a summary of the objectives, methods, and results of the modeling it had performed. Boehringer's responses further provide the FDA with Boehringer's conclusion that "upon review, the results of the simulation appeared to be unreliable."[21] The FDA determined not to direct a label change for Pradaxa based on the Boehringer company documents discussed in the Cohen articles.

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[20] The reference derives from the lead article by Deborah Cohen, the Investigations Editor for the BRITISH MEDICAL JOURNAL. Deborah Cohen, "Dabigatran: how the drug company withheld important analyses," BMJ 2014;349:g4670.

[21] On January 18, 2016, the EMA issued its final report regarding Boehringer and Pradaxa, concluding that "routine [therapeutic drug monitoring] of Pradaxa should not be recommended." On February 9, 2016, Boehringer transmitted the EMA's final report to the FDA.

f. The 2014 Chin article

On March 5, 2014, the BRITISH JOURNAL OF CLINICAL PHARMACOLOGY published an article[22] ("the Chin article") that proposed a "potential dosing algorithm" in which "[a]nticoagulant tests can be used to check for excessive effect" in certain patient subgroups after dosing based on certain patient characteristics like renal function. The Chin article broadly observed:

> As a result of the very strong relationship between dabigatran plasma concentrations and anticoagulant effects, monitoring of anticoagulant effects could assist in the management of patients at higher risk of thrombotic episodes and/or hemorrhage.
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> ***
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> Laboratories should be encouraged to set up the [ECT or dTT tests] because of the extremely strong linear relationship with dabigatran concentrations. A target range for the [dTT test], which corresponds to dabigatran plasma concentrations of 75–240 mg l-1, is 55 to 65s.

The Chin article stated that the suggested "approach could potentially offer a combination of greater therapeutic benefit and less risk of side effects" and that "[s]uch an approach lends itself to further clinical trials."

g. The 2015 CSRC meetings

In 2015, representatives from the FDA participated in two meetings of the Cardiac Safety Research Consortium ("CSRC") regarding the potential role of plasma monitoring for Pradaxa and other novel oral anticoagulants. The meeting generally concluded:

> Monitoring [novel oral anticoagulants] as a way to assess drug level/actions or to maximize dose flexibility or ultimately to benefit patient care remains unproven. Clinical outcome data are lacking.

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[22] Paul K.L. Chin, *et al.*, "A proposal for dose-adjustment of dabigatran etexilate in atrial fibrillation guided by thrombin time," BRIT. J. CLIN. PHARM. 2014; 78:599-609.

More specifically, the participants, including four senior FDA officials, reached a "consensus position[]" that "[r]outine PK-PD measurements to guide [novel oral anticoagulant] dosing cannot currently be recommended because of the lack of reliable tests, lack of clinical evidence of benefit, and lack of data to guide appropriate dosing."

4. Ridings' experience with Pradaxa

In February of 2012, taking into consideration that Ridings was then 77 years old, was on medication for hypertension, and had been diagnosed with AF, Dr. Gupta concluded[23] that Ridings was a candidate for anticoagulant medication and prescribed Pradaxa to be used in his treatment. On July 31, 2013, Ridings was admitted to the hospital for a subdural hematoma[24] and a neurosurgeon performed surgery to insert a subdural drain. Shortly thereafter, the doctor determined that Ridings had a tension pneumocephalus – a condition where air pressure builds within the skull and can result in serious injury. As a result of the development of this condition, the neurosurgeon performed two craniotomies on Ridings on August 9, 2013. Ridings and his wife contend that Boehringer "failed to provide an adequate warning of the dangerous characteristics of Pradaxa."

With the present lawsuit, Ridings contends that prior to his hospitalization in July of 2013, the warning label for Pradaxa should have contained some or all of the following warnings:

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[23] Medical professionals utilize a CHADS2 scoring system to evaluate patients diagnosed with AF as candidates for anticoagulant medication. The scoring system considers a patient's age and gender as well as any history of congestive heart failure, hypertension, diabetes, stroke and vascular disease. A score of "2" or more points indicates a patient may be a candidate for an anticoagulant. Dr. Gupta scored Ridings at a "3."

[24] A subdural hematoma is a collection of blood under the dura, one of the outer linings of the brain adjacent to the skull.

1. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors,

2. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information,

3. Coagulation test thresholds at trough that may be associated with an increased risk of bleeding,

4. A safe and effective Therapeutic Range exists between 40-215 ng/ml that optimizes benefit and risk,

5. Patients who have trough plasma concentrations at or above the 90th percentile, 215 ng/ml, are at an unnecessary risk of major bleeding events,

6. Failure to attain a plasma concentration in the therapeutic range may require discontinuation of therapy,

7. P-pg Inhibitor co-medication is a risk factor that increases the risk of bleeding; and

8. Gastroesophageal reflux may increase the hemorrhagic risk.

For purposes of the present consideration of federal preemption, the Court assumes, without deciding, that Ridings and his wife could otherwise prove all of the elements of a failure-to-warn personal injury action against Boehringer (*e.g.,* that the proposed different warning(s) would have caused Ridings to not start (or later discontinue) the use of Pradaxa.)

C. Conclusions of law

The doctrine of federal preemption finds its roots in the Supremacy Clause of the United States Constitution. U.S. CONST. art. VI, cl. 2. In general, the doctrine provides that:

> Where state and federal law "directly conflict," state law must give way. [And] state and federal law conflict where it is "impossible for a private party to comply with both state and federal requirements."

PLIVA, Inc. v. Mensing, 564 U.S. 604, 617–18, 131 S. Ct. 2567, 2577 (2011) (*citations omitted*). It is well-settled that the "state law" to be considered in cases of federal preemption includes not

only state statutes and regulations, but also a state's tort law. *Geier v. American Honda Motor Co.*, 529 U.S. 861, 886, 120 S. Ct. 1913, 1928 (2000). At the core of the doctrine of federal preemption is an acceptance of the supremacy of federal law and the potential unfairness in requiring a defendant to comply with both federal law and state law where such laws are fundamentally different, particularly where compliance with both may be impossible. In such cases, compliance with federal law prevails and a defendant cannot be held liable for "violating" the state law.

Tort litigation against the pharmaceutical industry often involves arguments for and against federal preemption inasmuch as:

> Under the 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act, 76 Stat. 780, 21 U.S.C. §§ 301, *et seq.* ("FDCA"), 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. Meeting those requirements involves costly and lengthy clinical testing.

Mensing, 564 U.S. at 612, 131 S. Ct. at 2574. *Mensing*, like the remaining claims in this case, involved claims regarding the adequacy of drug labeling.

Broadly speaking, under *Mensing* and similar cases, federal law preempts any state law claim requiring a drug manufacturer to change its labeling. However, the federal laws respecting drug labeling do provide some limited opportunities to a drug manufacturer to unilaterally change a drug label that can, in some cases, effectively undercut any claim of impossibility when it comes to compliance with both state and federal law and, thus, negate the application of federal preemption. As summarized by the Supreme Court:

> The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label.[25] Generally

[25] Through the FDA, the federal government regulates the manufacture, labeling, and sale of pharmaceuticals. 21 U.S.C. § 301, *et seq.* To bring a drug into the United States

> speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application. There is, however, an FDA regulation that permits a manufacturer to make certain changes to its label before receiving the agency's approval. Among other things, this "changes being effected" ("CBE") regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

Wyeth v. Levine, 555 U.S. 555, 568, 129 S. Ct. 1187, 1196 (2009) (*citing* 21 C.F.R. § 314.70(c)(6)(iii)).[26] The referenced CBE regulation may only be utilized by a drug manufacturer to change its label "to reflect newly acquired information." 73 Fed. Reg. 49609. Such "'newly acquired information' is not limited to new data, but also encompasses 'new analyses of previously submitted data.'" 73 Fed. Reg. 49604. As explained by the Supreme Court:

> The 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: "[I]f the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for 'newly acquired information.'"

Levine, 555 U.S. at 569, 129 S. Ct. at 1197 (*quoting*, *in part*, 73 Fed. Reg. 49607)).

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market, a manufacturer must file a new drug application with the FDA, explaining the testing and studies performed on the drug by the manufacturer and demonstrating that the drug is "safe for use under the conditions prescribed." 21 U.S.C. § 355(b)(1)(A), (b)(1)(F). In addition, the manufacturer must include proposed labeling language. 21 U.S.C. § 355(d). The FDA's approval of a new drug application includes the approval of the exact text in the proposed label, although the FDA can direct a manufacturer to change a drug's label after it has entered the market. 21 U.S.C. § 355(o)(4).

[26] With the adoption of the CBE regulation, the FDA "adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Levine*, 555 U.S. at 568, 129 S. Ct. at 1196.

In light of the CBE regulation, the Supreme Court in *Levine* determined that a "[drug] manufacturer [bears the] ultimate responsibility for its label, [the CBE regulation] provides a mechanism for adding safety information to the label prior to FDA approval, [and] when the risk of [a new danger from the drug becomes] apparent, [the manufacturer has] a duty to provide a warning that adequately describes that risk." *Levine*, 555 U.S. at 571, 129 S. Ct. at 1198. Fundamentally, then, the Court found that compliance with both federal law and state law could not be deemed impossible as a matter of law. However, the Court did note that impossibility could still apply (and thus federal preemption would bar the state law action) if a manufacturer could show by "clear evidence that the FDA would not have approved a change to [the drug's] label." *Id*.

As previously discussed, the Court in *Merck Sharp & Dohme v. Albrecht*, 139 S. Ct. 1668 (2019), further addressed the preemption of failure-to-warn claims in pharmaceutical product liability litigation. In *Albrecht*, the Court found:

> We turn now to what is the determinative question before us: Is the question of [federal preemption in a failure-to-warn case involving a regulated pharmaceutical] primarily one of fact, normally for juries to decide, or is it a question of law, normally for a judge to decide without a jury? [W]e answer this question by concluding that the question is a legal one for the judge, not a jury.

Albrecht, 139 S. Ct. at 1679. The Court further explained:

> The underlying question for this type of impossibility pre-emption defense 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. And, of course, in order to succeed with that defense the manufacturer must show that the answer to this question is yes.

Id. at 1678 (acknowledging "that meeting the standard [is] difficult, but [noting that] impossibility pre-emption is a demanding defense"). Moreover, "the "possibility of impossibility [is] not enough." *Id*.

Based upon the guidance of the Supreme Court, this Court must next analyze the evidence[27] offered at the hearing on the issue of federal preemption in two stages:

(1) First, did Ridings show that "newly acquired information" existed such that Boehringer could have unilaterally changed its label for Pradaxa in accordance with the CBE regulation; and

(2) If Ridings did establish the existence of such newly acquired information, did Boehringer establish an impossibility preemption defense by presenting "clear evidence" that the FDA would have rejected such labeling change.

In *Albrecht*, the Court offered some further – albeit cryptic – guidance. On one hand, the Court noted:

> We understand that sometimes contested brute facts will prove relevant to a court's legal determination about the meaning and effect of an agency decision. For example, if the FDA rejected a drug manufacturer's supplemental application to change a drug label on the ground that the information supporting the application was insufficient to warrant a labeling change, the meaning and scope of that decision might depend on what information the FDA had before it. Yet in litigation between a drug consumer and a drug manufacturer (which will ordinarily lack an official administrative record for an FDA decision), the litigants may dispute whether the drug manufacturer submitted all material information to the FDA. [I]n those contexts where we have determined that the question is "for the judge and not the jury," we have also held that "courts may have to resolve subsidiary factual disputes" that are part and parcel of the broader legal question.

Albrecht, 139 S. Ct. at 1680.

[27] In *Albrecht*, the Court acknowledged that the determination of preemption will often require the Court to make factual determinations based on competing and contradictory evidence.

> [T]he FDA's CBE regulation – permits drug manufacturers to change a label to "reflect newly acquired information" if the changes "add or strengthen a ... warning" for which there is "evidence of a causal association," without prior approval from the FDA. Of course, the FDA reviews CBE submissions and can reject label changes even after the manufacturer has made them. And manufacturers cannot propose a change that is not based on reasonable evidence. But in the interim, the CBE regulation permits changes, so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both.[28]

Id. at 1668 (*emphasis added*). On the other hand, the Court also found, "We do not further define [the] use of the words "clear evidence" in terms of evidentiary standards, such as "preponderance of the evidence" or "clear and convincing evidence" and so forth, because . . . [a] judge must simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflict.'" *Id*.

Turning first to the issue of "newly acquired information," the Court considers whether there is adequate proof that Boehringer was in possession of such information, and that such information was reasonable evidence of an association of a serious hazard with Pradaxa sufficient to require Boehringer to unilaterally revise its label to include a warning. The Court concludes that the evidence presented in the preemption hearing falls short of the requisite level

[28] The *Albrecht*'s court's use of the work "ordinarily" arguably seems to imply that preemption is the exception in product liability drug litigation involving labeling claims. However, later in its opinion, the Court notes that that only "when the risks of a particular drug become apparent, [does] the manufacturer ha[ve] a duty to provide a warning that adequately describes the risk." *Id*. at 1677 (*emphasis added*). The FDA, on the other hand, applies an intermediate test, noting it "would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event." *Supplemental Application Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 FED. REG. 2848, 2851 (Jan. 16, 2008). *See also Wyeth*, 555 U.S. at 571, 129 S. Ct. at ---- ("requiring a manufacturer to revise its label to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"). The Court will utilize the Wyeth court's formulation herein.

of proof to establish such a requirement. "Newly acquired information" under the CBE regulation includes "data, analyses, or other information not previously submitted to the FDA, which may include (but is 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 the FDA." *Utts v. Bristol-Myers Squibb Co.*, 251 F.Supp.3d 644, 659 (S.D.N.Y. 2017) (*citing* 21 C.F.R. § 314.70(c)(6)(iii)). As noted, such newly acquired information "must provide reasonable evidence of a causal association of a clinically significant adverse reaction linked to a drug." 21 C.F.R. § 201.57(c)(6)(i) (*emphasis added*). A clinically significant adverse reaction "ha[s] a significant impact on therapeutic decision-making, such as a risk that is potentially fatal or otherwise serious." 21 C.F.R. § 201.57(c)(6)(i) (*emphasis added*).[29] As a result:

> [T]he CBE regulation requires that there be sufficient evidence of a causal association between the drug and the information sought to be added.

McGrath v. Bayer HealthCare Pharm. Inc., 393 F. Supp. 3d 161, 167 (E.D.N.Y. 2019)

To ensure that only "scientifically accurate information appears in the approved labeling" the FDA prefers a cautious approach and finds that because "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance," there must be "sufficient evidence of a causal association between the drug and

[29] The FDA imposes this standard because it "recognize[s] that exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug ... or decrease the usefulness and accessibility of important information by diluting or obscuring it. Indeed, labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance." *Utts*, 251 F.Supp.3d at 659 (*emphasis added*) (*citing* 73 FED. REG. 2848, 2851 (Jan. 16, 2008)).

the information sought to be added." *Utts*, 251 F.Supp.3d at 659 (*emphasis added*). Consequently, studies concluding that it "remains unknown" whether a drug is linked to a particular adverse reaction or risk or that "further studies are required to address possible clinical consequences" do not constitute reasonable or well-grounded scientific evidence of "clinically significant adverse effects" under the CBE regulation. To find otherwise would permit the "inclusion of speculative or hypothetical risks" absent "sufficient evidence of a causal association" between the subject drug and the risks associated with the drug's use.

By and large, nearly all of the "newly acquired information" at issue here still relies upon the underlying RE-LY plasma concentration data and reflects information – for all intents and purposes – that was provided to the FDA at the time of the initial approval of Pradaxa for the American market. With that information in 2010, the FDA understood that the use of Pradaxa presented a trade-off between an increased risk of stroke and an increased risk of major bleeding. And that these competing risks could be partly addressed by Pradaxa dosage amount and/or by plasma concentration monitoring. With that information, the FDA made a determination about Pradaxa dosage and came to a decision to include only a generalized recommendation regarding plasma concentration monitoring.

Nonetheless, it is clear that "newly acquired information" may encompass a new analysis of "old" data. Such an approach:

> 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: [I]f the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for '"newly acquired information."

Wyeth, 555 U.S. at 569, 129 S. Ct. at 1197. But, even with this understanding, "studies published after a plaintiff's injury [are not] relevant to constitute newly acquired information." *Roberto v. Boehringer Ingelheim Pharm., Inc.*, 2019 WL 5068452, at *14 (Conn. Super. Ct. Sept. 11, 2019).

Based on the latter reasoning, the Court does not find the Chin article published on March 5, 2014 (proposing a "potential dosing algorithm" in which "[a]nticoagulant tests can be used to check for excessive effect") or the 2015 meeting of the CSRC (regarding the potential role of plasma monitoring for Pradaxa and other novel oral anticoagulants) to constitute even *prima facie* "newly acquired information." However, the Court will examine whether the following constitute "newly acquired evidence" under the CBE regulation:

(1) the 2011 issuance of the more-detailed Pradaxa label in the EU,

(2) Boehringer's July 15, 2011 Clinical Overview Statement,

(3) Boehringer's 2012 computer simulation findings,

(4) the 2013 Reilly paper,[30] and

(5) the 2014 BRITISH MEDICAL JOURNAL articles – to the extent the articles reflect and/or discuss information known to Boehringer prior to July of 2013 that was not shared with the FDA.

[30] The Reilly paper was not published until February of 2014, but it was submitted for publication in July of 2013 (the same month that Ridings was hospitalized). Inasmuch as the paper was co-authored by Boehringer employees, there is a reasonable evidentiary inference that the information in the published Reilly paper was known to Boehringer prior to July of 2013. For purposes of this order, the Court will assume that the inference is sufficient to treat the Reilly paper as sufficiently predating Ridings' hospitalization to warrant consideration as "newly acquired information."

Ridings argues to the Court that the "Euro Label" differs in significant ways from the labeling for Pradaxa approved by the FDA.[31] Consequently, Ridings reasons that "reasonable evidence existed that would have allowed Boehringer to change its US label." The proposition may be true, but it only addresses a part of the preemption analysis. While "reasonable evidence" may exist to support the Euro Label – if substantially similar "reasonable evidence" was presented to the FDA and that agency determined not to give different or more expansive warnings, then Boehringer is still entitled to rely upon the defense of federal preemption. Specifically, a claim that a drug label should be changed based solely on the "information previously submitted to the FDA is preempted because the CBE regulation cannot be used to make a label change based on such information." *In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Product Liability Litigation,* 185 F.Supp.3d 761, 769 (D.S.C. 2016). *See also Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 815 (7th Cir. 2018) (2019) (plaintiff's claim of newly acquired information "fails because the undisputed evidence shows that the FDA was aware of the nature of the data it received from" the manufacturer and a subsequent published article merely contained the same study the manufacturer had submitted to the FDA); 21 C.F.R. § 314.3 ("Newly acquired information is data, analyses, or other information not previously submitted to the Agency").

Moreover, at least under the facts of the present case, the Court concludes that the actual warnings approved for a foreign label are not in and of themselves newly acquired evidence when they are based on consideration of substantially similar information. Foreign drug labeling is the product of different and distinct regulatory standards and decisions. As a consequence,

[31] Several of Ridings' proposed "additional" warnings are similar to warnings in the Euro Label and three of Ridings' five "plasma concentration" warnings are taken verbatim from the Euro Label.

courts routinely hold that "[t]he mere existence of a differently structured and written European label does not establish that the U.S. label is insufficient, misleading, or legally inadequate." *McDowell v. Eli Lilly & Co.*, 2015 WL 845720, op. at *5 (S.D.N.Y. Feb. 26, 2015). *See also Meridia Prod. Liability Litigation v. Abbott Labs.*, 447 F.3d 861, 867 (6th Cir. 2006) (declining to consider argument that US label was inadequate based on fact that "the warning label for [the drug's] European equivalent contained more detailed instructions for the treating physician").

The Court also concludes that Boehringer's July 15, 2011 Clinical Overview Statement does not constitute newly acquired evidence for purposes of the CBE regulation. With regard to the 2011 COS, Ridings in particular points to two statements in the document:

> Based on the clotting times determined by the [dTT test] at concentrations of 215 ng/mL in the above mentioned studies, a diluted thrombin clotting time of >65 sec at trough (as given in the [European] prescribers guide) is considered to represent a conservatively assessed cut-off value**.**
>
> The 90th percentile of trough ECT after 150 mg BID as observed in RE-LY was 103 s [RE-LY, U09-3249-02] and therefore, exceeding a 3-4 fold elevated level compared to baseline will likely be associated with a higher risk of bleeding.
> Based on these statements, Ridings asserts the 2011 COS establishes "a different and greater risk" of bleeding based on Pradaxa blood levels than is conveyed in the US label.

These passages are drawn from the Euro Label. In fact, the evidence shows that the 2011 COS was prepared by Boehringer as a "reference document" for the Pradaxa Prescriber Guide, an EMA publication recommending use of the 110 mg dose of Pradaxa for certain individuals. As such, "it is arguable whether the statement[s] in question constitute '[D]ata, analyses, or other information' within the meaning of the CBE regulation." *Roberto*, op. at *18 ("The passage [relied upon by the plaintiff] appears to be merely a recitation of what [Boehringer] will include in the European label, presumably in order to comply with European requirements.").

Moreover, like the court in *Roberto*, this Court finds that the substantive information contained in the 2011 COS was known to the FDA through the submission of relevant data and studies by Boehringer. *Id*. "[T]he FDA was already well aware of the association between high blood plasma concentrations of Pradaxa and the increased risk of bleeding."). Specifically, the information in the 2011 COS is substantially similar to the information provided by Boehringer to the FDA prior to its approval of Pradaxa. At that time, Boehringer noted to the FDA that an analysis of the RE-LY data showed that "the risk of 93.0 ng/mL to 7.5% and hence be almost doubled at 215 ng/mL, the 90th percentile of measured trough concentrations." And Boehringer, more broadly, also informed the FDA that "aPTTs above 80 sec were associated with a higher major bleed rate" and an "ECT [test] displayed a linear relationship with dabigatran standard concentrations." Indeed, the April 2013 FDA-approved label for Pradaxa provided:

> The aPTT test provides an approximation of PRADAXA's anticoagulant effect. The average time course for effects on aPTT, following approved dosing regimens in patients with various degrees of renal impairment is shown in Figure 1. The curves represent mean levels without confidence intervals; variations should be expected when measuring aPTT. While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, the curves can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of PRADAXA is not precisely known. In the RE-LY trial, the median (10th to 90th percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds.
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> ***
>
> The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than activated partial thromboplastin time (aPTT). In the RE-LY trial, the median (10th to 90th percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds.

The Court concludes that the blood concentration data in the 2011 COS does not reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA and, as such, does not constitute newly acquired evidence.

With regard to Boehringer's 2012 computer simulations, Ridings does not seemingly dispute the determination by Boehringer that the modeling was ultimately found to be flawed when compared to the experiences of actual patients in the RE-LY study. Instead, Ridings focuses on the fact that after obtaining the initial results from the computer simulation, Boehringer sought a patent for a proposed dose-titration method. As testified to by Ridings expert, Laura Plunket:

> So this is the idea that if you have a – if you believe it's important enough to protect, then I don't understand why you don't give this information to physicians.

Ridings essentially argues that – by seeking a patent – Boehringer believed it had "reliable scientific information" and such information constitutes "newly acquired information."

One of the difficulties in analyzing the concepts of "relevancy" and "reasonableness" in determining when "newly acquired evidence" has been established is the undeniable fact that scientific research does not advance in a progressively linear fashion. Ideas are hatched and then tested. Sometimes the ideas advance scientific progress, other times new ideas are found to be flawed non-starters. Nonetheless, the rejection of bad ideas is as important to the process as the confirmation and embracing of good ideas. Based on the evidence presented, the Court concludes that Boehringer's computer simulation testing was a bad idea that simply did not pan out. It does not constitute newly acquired evidence under the CBE regulation.

The final two purported examples of "newly acquired information" present more difficult analyses. With regard to the Reilly paper, the courts have split on whether it constitutes "newly acquired information" under the CBE regulation. In *Knight v. Boehringer Ingelheim Pharm., Inc.*, 2019 WL 2144812, at *5 (S.D.W. Va. May 15, 2019), the Court found that the Reilly paper constituted "newly acquired information" based largely on admissions made by Boehringer in that case:

> [Boehringer] acknowledges that the Reilly exposure-response paper was published after Pradaxa's approval." [And d]uring trial, [Boehringer] agreed that new analyses were done, and believed that whether there was "newly acquired information" is a fact that should indeed be decided by a jury [arguing:] "We have some new analysis that was done. There's no question about it. And I think there's probably a fact issue on whether there's newly acquired information or newly acquired analysis that warranted a change."

Id at *4-5.[32] By contrast, in the *Roberto* case, the court – in a detailed analysis – found that the Reilly paper did not "constitute newly acquired information." *Roberto,* op. at *17. The Court largely agrees with the analysis in *Roberto*.

The Court finds, as did both the *Knight* and *Roberto* courts, that the Reilly paper is a work of sufficient reliability or substance to satisfy the definition of "newly acquired information" contemplated by 21 C.F.R. § 314.3 ("[D]ata, analyses, or other information not previously submitted to the [FDA], which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data,

[32] The Court does not consider the "admission" of Boehringer in the *Knight* case to impact this preemption question at issue in this order. First and foremost, in *Knight*, Boehringer was merely stating that a reasonable fact question existed as to whether the "new analysis" reflected in the Reilly paper was "newly acquired information" under the CBE regulation. The proceedings in *Knight* was occurring prior to the Supreme Court in *Albrecht*. That later case has made it clear that the issues to be determined for application of federal preemption are for the Court to decide, not a jury, even if such determination requires the resolution of factual disputes.

e.g., meta-analyses."). Specifically, the Reilly paper addresses a "new analysis of previously submitted data." Consequently, the critical issue is whether the new analysis in the Reilly paper discloses "risks of a different type or greater severity or frequency than previously included in submissions to FDA."

The Reilly paper includes an introduction that sets out the primary objective of the authors:

> The goal of this study was to analyze the impact of dabigatran plasma concentrations, patient demographics, and aspirin (ASA) use on frequencies of ischemic strokes/systemic emboli and major bleeds in atrial fibrillation patients.

To that end, the Reilly paper noted that "[t]he efficacy and safety of dabigatran etexilate were demonstrated in the RE-LY . . . trial, but a therapeutic concentration range has not been defined." Moreover, the article stated at the outset that it was currently "unknown whether there [was] a single concentration range where the balance between thromboembolic events [strokes] and bleeding events is optimal for all AF [atrial fibrillation] patients." After an extensive analysis, the Reilly paper concludes:

> Both doses [110 mg and 150 mg] of [dabigatran etexilate] in RE-LY were associated with a more than 5-fold variation in plasma concentrations, indicating a wide therapeutic range. Renal function[33] was the predominant patient characteristic that determined plasma concentrations. Safety and efficacy outcomes were correlated with plasma concentrations of dabigatran, with age as the most important covariate. There is no single plasma concentration range that provides optimal benefit-risk for all patients. The balance between stroke risk and bleed risk varied with concentration, suggesting that there is a subset of AF patients who may improve their benefit-risk balance with [dabigatran etexilate] by a tailoring of the dose in relation to patient characteristics.

[33] Even prior to the Reilly paper, the FDA-approved dosage and labeling had already addressed renal functionality, by providing for the availability of a 75 mg dose of Pradaxa for patients with severe renal impairment.

In light of the overall conclusion of the Reilly paper that "[t]here is no single plasma concentration range[34] that provides optimal benefit-risk for all patients," the Court concludes that the article does not establish any "risks of a different type or greater severity or frequency than previously included in submissions to FDA." As noted by the *Roberto* court:

> [T]he [Reilly paper] essentially concludes that it is not possible to identify a group of patients with specific concentrations of Pradaxa in their blood plasma who are at an unacceptable risk of bleeding relative to the need to reduce the risk of stroke. Because the Reilly paper does not identify any specific plasma concentration levels that pose "risks of a different type or greater severity or frequency than previously included in submissions to FDA," the Reilly paper does not constitute newly acquired information.

Id. at *16.

Finally, the Court turns to the 2014 BRITISH MEDICAL JOURNAL articles, collectively referred to as the Cohen articles. While these articles were published after 2013, the articles focus on documents (early drafts of the Reilly paper and emails surrounding the drafting) that predate Ridings' hospitalization. Moreover, the articles assert that information in those documents was withheld from the FDA by Boehringer. It seems axiomatic that a drug manufacturer cannot defeat a claim of "newly acquired information" based simply on the temporal fact that information predates action by the FDA if the manufacturer never shared the information with the FDA. However, the question still remains as to whether the information so "disclosed" in the articles was of sufficient reliability or substance and involved "risks of a different type or greater severity or frequency than previously included in submissions to FDA."

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[34] The Reilly paper does include the finding: "Across the 10th to 90th percentile range of steady-state trough plasma concentrations achieved for the 150 mg bid [twice a day] dose, the overall risk of major bleeding during the trial ranges from approximately 2% to 7% (approximately 1.0% to 3.5% per year)." As previously discussed herein, the FDA was aware of this correlation dating back to the original Boehringer submissions for Pradaxa in 2010.

The Court concludes the arguably relevant information in the Cohen articles – the various emails, documents, comments, and discussions concerning potential therapeutic ranges in early drafts of the Reilly paper – does not meet these thresholds. Again as noted by the *Roberto* court:

> These preliminary discussions do not provide reliable evidence of new risks. They are essentially uncorroborated trial balloons. To be sure, it is fully appropriate for a scientific dialogue to take place, and disagreement to occur, during the drafting of a major paper. There is no reason to believe that the process of drafting and finalizing a scientific paper does not benefit from the same type of advocacy, examination, and argument that is the hallmark of our own judicial system. In both cases, the decision is better because the opposition was heard. But, ultimately, a preliminary opinion or dissenting voice is just that—it is not a final opinion.

Id. at *16.

Based on the foregoing, the Court finds that Ridings has not met his burden of establishing sufficient evidence of "newly acquired information" so to allow the Court to conclude that Boehringer could and should have availed itself of the applicable federal regulations and unilaterally (*i.e.*, in advance of FDA authorization) given any of the warning(s) advocated by Ridings.

In light of the Court's conclusion on "newly acquired information," a determination on the second issue for federal preemption is not required. Nonetheless, in the interests of judicial efficiency, the Court will briefly address the issue. Based on the record submitted, the Court concludes that the Boehringer offered sufficient "clear evidence" that the FDA – even if presented with all of Ridings' suggested "newly acquired information" – nonetheless would have rejected the warning(s) advocated by Ridings.

The meaning and application of the Supreme Court's mandate that a drug manufacturer establish its position by "clear evidence" has left many courts confused. In *Albrecht*, the Court did note:

> We do not further define [the] use of the words "clear evidence" in terms of evidentiary standards, such as "preponderance of the evidence" or "clear and convincing evidence" and so forth, because . . . [a] judge must simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflict.'"

Albrecht, 139 S. Ct. at 1668. Applying this "standard" to the record herein, the Court finds that Boehringer's evidence was "clear evidence." Central to the Court's conclusion are two pertinent underlying facts:

(1) the warnings being advocated for by Ridings involve risks that are – to some degree – addressed in the FDA's current labeling (*i.e.*, the failure-to-warn in this case goes to the qualitative extent of the warning, not to a claim of an outright failure to recognize a particular risk);

(2) even if the information relied upon and noted by Ridings is deemed to be "newly acquired information" for purposes of the CBE regulation, such information has been provided to the FDA and the FDA has not taken any action to substantively alter Pradaxa's warning on the topics at issue in this litigation.

On the second point, the Court wishes to be clear – it should not always be the case that simple inaction by the FDA in light of submitted data will always be "clear evidence" that the FDA would reject a particular warning. In this case, however, in light of the known issues and the ongoing give-and-take between Boehringer and the FDA on these issues (in particular, plasma concentration monitoring), the FDA's continued inaction does represent clear evidence under these facts.

D. Ridings' motion to exclude Boehringer's expert testimony

The Court now turns to a final residual issue. Pending before the Court is Ridings' motion regarding some of the evidence presented by Boehringer [Doc. 229]. In the motion, Ridings objects to Boehringer's use of deposition testimony obtained from witnesses Jeffrey Friedman, Paul Reilly, Klaus Dugi and Jorge Kreuzer because the depositions were taken in other cases, albeit other cases involving Pradaxa and product liability claims against Boehringer. In the case of two of those individuals (Drs. Friedman and Reilly), Ridings himself designated deposition testimony taken in other Pradaxa litigation. The Court understands that sworn testimony may be used against a party in circumstances where the party could not affirmatively offer such testimony. Specifically, under FED. R. EVID. 801(d)(2)(D), the statements of Boehringer's employees may be used by Ridings as statements of a party opponent and thus not hearsay. By contrast, Boehringer generally may offer such statements of its own employees – even sworn deposition testimony – into evidence only if the declarant is unavailable. FED. R. EVID. 804(b)(1). Boehringer does not attempt to establish unavailability. Instead, Boehringer notes that the federal courts – including the Eighth Circuit – have construed the Federal Rules of Civil Procedure to encompass an additional exception to the hearsay rule. To that end, the Federal Rules relevant to use of deposition testimony in court testimony provide:

> At a hearing or trial, all or part of a deposition may be used against a party on these conditions:
>
> (A) the party was present or represented at the taking of the deposition or had reasonable notice of it;
>
> (B) it is used to the extent it would be admissible under the Federal Rules of Evidence if the deponent were present and testifying; and
>
> (C) the use is allowed by Rule 32(a)(2) through (8).

FED. R. CIV. P. 32(a)(1). Of relevance to the third condition, the Rule further provides:

> A deposition lawfully taken and, if required, filed in any federal- or state-court action may be used in a later action involving the same subject matter between the same parties, or their representatives or successors in interest, to the same extent as if taken in the later action. A deposition previously taken may also be used as allowed by the Federal Rules of Evidence.

FED. R. CIV. P. 32(a)(8).

In *Fletcher v. Tomlinson*, 895 F.3d 1010 (8th Cir. 2018), the Court joined with other federal courts in finding that "Rule 32(a) is an independent exception to the hearsay rule." *Id*. at 1020, 1020 n.9. The Court agrees that Rule 32(a) may serve as a basis for admissibility irrespective of the Federal Rules of Evidence. However, the Court is less convinced that Boehringer satisfies the requirements for Rule 32(a)(1)(A). The Court does not question that Ridings' counsel may have been present at the subject depositions, but is not necessarily convinced that this fact (or the fact that the subject matter in those other lawsuits was the same as in this litigation) equates to the party being "present or represented at the taking of the deposition." However, for the reasons set out below distinguishing a jury trial and a Court hearing on a preliminary legal question, the Court does not find any harmful error arising from the use of the identified depositions by Boehringer.

The more substantive objection raised in Ridings' motion concerns the live in-court testimony submitted by Boehringer from Maureen Oakes. Ridings objects that Dr. Oakes was not disclosed as an expert witness in Boehringer's discovery disclosures, Boehringer did not disclose Dr. Oakes on its witness list in July of 2019 (when the matter was still set for a jury trial), and did not disclose that Dr. Oakes would be testifying in any capacity until one week prior to the commencement of the Court's hearing on the preemption issue. Ridings wishes to have Dr. Oakes' testimony stricken.

The Court denies the motion to exclude and/or strike Dr. Oakes' testimony. The Court nonetheless is sympathetic to Ridings' objections. Boehringer committed considerable resources (including attorney manpower) to this litigation. The failure to identify Dr. Oakes at all – even if the Court accepted the rationale that she was merely a corporate representative who did not offer expert testimony – until just prior to the preemption hearing is almost inexcusable. To be clear, had this matter proceeded to a jury trial as originally planned, Dr. Oakes' testimony likely would have been excluded as an unfair surprise. Because the hearing, instead, was tried to the Court on a preliminary legal issue,[35] the Court is more inclined to relax the rules and focus on two broad questions:

> (1) was the content of the testimony of Dr. Oakes a "surprise" to Ridings such that the ability to cross-examine was substantively undermined; and
>
> (2) was the late disclosure of Dr. Oakes negligent oversight by Boehringer or an effort to deliberately sandbag.

As to the first issue, the Court believes that Ridings' legal team was not surprised by Dr. Oakes' testimony and, in fact, conducted an effective and meaningful cross-examination. As to the second question, the Court finds no evidence of any deliberate effort to conceal Dr. Oakes' identity from the Court or Ridings.

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[35] Even in cases on a nonjury trial on all issues, evidentiary objections play only a "limited role" *Patel v. Patel*, 2019 WL 758609, op. at *1 (W.D. Okla. Feb. 20, 2019). The Eighth Circuit has bluntly held:

> In the trial of a nonjury case, it is virtually impossible for a trial judge to commit reversible error by receiving incompetent evidence, whether objected to or not.

Builders Steel Co. v. Commissioner, 179 F.2d 377, 379 (8th Cir. 1950). *See also Murray v. United States*, 117 F.2d 40, 45 (8th Cir. 1941) ("[I]t is assumed that the court [sitting as a factfinder] considered only competent and material evidence.").

In accordance with the foregoing discussion, it is

ORDERED that it is the finding of this Court that all of Ridings' remaining claims are preempted by federal law and summary judgment in favor of Boehringer is GRANTED.

/s/ John T. Maughmer
John T. Maughmer
United States Magistrate Judge