NO. X03 HHD CV17-6075319S	:	STATE OF CONNECTICUT
TAMRA LEA KEARNS ESTEP, REPRESENTATIVE OF THE ESTATE OF MYRNA KEARNS, DECEASED	:	SUPERIOR COURT
v.	:	COMPLEX LITIGATION DOCKET
	:	JUDICIAL DISTRICT OF HARTFORD
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., ET AL.	:	AUGUST 25, 2020

Ruling on Motion for Summary Judgment

Defendants Boehringer Ingelheim Pharmaceuticals, Inc., and Boehringer Ingelheim International GMBH (defendants or BI) move for summary judgment in this Pradaxa product liability case brought by the plaintiff, Tamra Lea Kearns Estep, who is the representative of the estate of decedent Myrna Kearns. The issue is whether federal law preempts the plaintiff's state law failure to warn claims. The court heard oral argument on July 20, 2020.

I

For purposes of summary judgment, the historical facts are undisputed. The plaintiff's decedent, Myrna Kearns, was a resident of St. Albans, West Virginia. The defendants, a German pharmaceutical company and its U.S. headquarters in Ridgefield, Connecticut, manufacture an anticoagulant medication called Pradaxa. Pradaxa is designed to prevent stroke in certain patients with atrial fibrillation, which is an irregular heart rhythm.

Mrs. Kearns' medical records reflect a history of gastroesophageal reflux disease, commonly referred to as GERD. In December, 2014, Mrs. Kearns was prescribed Pradaxa for the treatment of atrial fibrillation. On or about February 19, 2015, Mrs. Kearns, then age 72, suffered

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an upper gastrointestinal bleeding event for which she was hospitalized for approximately four days. Mrs. Kearns never fully recovered from the bleeding injury and passed away on March 9, 2015. Her death certificate lists "gastrointestinal bleeding" as a cause of death.

The plaintiff, the estate representative of the decedent, alleges in her amended complaint that the use of Pradaxa was a substantial contributing factor in causing or exacerbating the decedent's bleeding event and in causing her death. (Entry # 121.00.) The plaintiff also claims that the defendants did not provide warnings on the label[1] that adequately warned doctors prescribing Pradaxa about the risks of bleeding in patients with a history of preexisting GERD.[2] More specifically, the plaintiff asserts that "had the Defendants properly warned Mrs. Kearns' physicians that Pradaxa patients with preexisting GERD have an increased risk of major gastrointestinal bleeding, Mrs. Kearns would not have taken Pradaxa and would not have suffered the fatal bleeding event at issue in this case." (*Connecticut Consolidated Pradaxa Docket*, X03-

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[1]The United States Supreme Court has stated: "Although we commonly understand a drug's 'label' to refer to the sticker affixed to a prescription bottle, in this context the term refers more broadly to the written material that is sent to the physician who prescribes the drug and the written material that comes with the prescription bottle when the drug is handed to the patient at the pharmacy.... These (often lengthy) package inserts contain detailed information about the drug's medical uses and health risks." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672-73 (2019).

[2]Connecticut law, which applies in this case, employs the "learned intermediary" doctrine, in which "adequate warnings to prescribing physicians obviate the need for manufacturers of prescription products to warn ultimate consumers directly. The doctrine is based on the principle that prescribing physicians act as learned intermediaries between a manufacturer and consumer and, therefore, stand in the best position to evaluate a patient's needs and assess [the] risks and benefits of a particular course of treatment." (Internal quotation marks omitted.) *Vitanza v. Upjohn Co.*, 257 Conn. 365, 376, 778 A.2d 829 (2001)

HHD-CV135036974S, Entry #305.00.)[3]

The defendants move for summary judgment on the ground that federal law preempts the plaintiff's state law claims.

II

The Supremacy Clause of the federal constitution establishes that federal law "shall be the supreme Law of the Land ... any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const., art. VI, cl. 2. "Where state and federal law 'directly conflict,' state law must give way..... [The United States Supreme Court has] held that state and federal law conflict where it is 'impossible for a private party to comply with both state and federal requirements.'" (Citations omitted.) *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 617-18 (2011). The defendants here invoke this type of impossibility preemption. They assert that prevailing federal law – here federal regulations – made it impossible for the defendants to conform to the plaintiff's state law claims. See generally *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 707-08 (2d Cir. 2019). See also *Wyeth v. Levine*, 555 U.S. 555, 576 (2009) (Under the Supremacy Clause, an "agency regulation with the force of law can pre-empt conflicting state requirements.")

There is, to be sure, a presumption against federal preemption. See *Puerto Rico v. Franklin California Tax-Free Trust*, 136 S. Ct. 1938, 1946 (2016); *Wyeth v. Levine*, supra, 555 U.S. 565 n.3. Thus, "[i]n all pre-emption cases, and particularly in those in which Congress has

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[3]The Consolidated Pradaxa Docket contains about 2800 cases filed in the Hartford Judicial District alleging that the defendants failed to include adequate warnings on the Pradaxa label. This case falls into Group B under Case Management Order (CMO) 23, in which the plaintiff agreed to raise claims other than the claim that the label should contain additional warnings and advice about high blood plasma concentrations of Pradaxa or the need to monitor Pradaxa blood plasma levels. (Entry # 292.00.)

legislated ... in a field which the States have traditionally occupied, ... we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." (Internal quotation marks omitted.) *Wyeth v. Levine*, supra, 565. Impossibility preemption is therefore a "demanding defense"; (internal quotation marks omitted) *PLIVA, Inc. v. Mensing*, supra, 564 U.S. 634; and the "possibility of impossibility is not enough." Id., 635.

In this case, the defendants posit that the "CBE" regulations promulgated under the federal Food, Drug and Cosmetic Act (FDCA); 21 U.S.C. §301 et seq; made it impossible to change the Pradaxa label to meet the plaintiff's state law claims of failure to warn. The Second Circuit has explained the law concerning the CBE regulations in the following way. "The FDA can direct a pharmaceutical manufacturer to change a drug's label after it has entered the market, see 21 U.S.C. § 355(o)(4), but manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times .... Nevertheless, drug manufacturers are limited in their ability to unilaterally change the labels on their products. Specifically, to make a change on their own, a manufacturer must comply with the 'changes being effected' or 'CBE' regulation, set forth at 21 C.F.R. §314.70(c)(6)(iii). That regulation 'allows drug manufacturers to change [a label] without the FDA's preapproval if the changes "add or strengthen a contraindication, warning, precaution, or adverse reaction," or "add or strengthen an instruction about dosing and administration that is intended to increase the safe usage of the drug product," in order to "reflect newly acquired information."'" (Emphasis added.) *Gibbons v. Bristol-Myers Squibb Co.*, supra, 919 F.3d 707.[4]

[4]The actual CBE regulation is lengthy and complex. 21 C.F.R. § 314.70 is entitled: "Supplements and other changes to an approved NDA." Subsection (c) is entitled: "Changes requiring supplement submission at least 30 days prior to distribution of the drug product made

In *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019) (*Albrecht*), the United States Supreme Court recently added the following information. "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., 1678. "[F]ederal law—the 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. 21 C.F.R. § 314.70(c)(6)(iii)(A). Of course, the FDA reviews CBE submissions and can reject label changes even after the manufacturer has made them. See §§ 314.70(c)(6), (7). And manufacturers cannot propose a change that is not based on reasonable evidence. § 314.70(c)(6)(iii)(A). 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." Id., 1679; see note 4 supra.

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using the change (moderate changes)." Paragraph 6 provides: "The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:" Subparagraph (iii) (A) through (C) then provides as follows: "Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following: (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter; (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product ...."

From this recital, it is apparent that the phrase "newly acquired information" is a key component of the CBE regulation. "Because manufacturers may unilaterally update a drug's label if the change complies with the CBE regulation, a state law failure-to-warn claim that depends on newly acquired information – information that Defendants could have added to their label without FDA approval – is not preempted." (Internal citations omitted; internal quotation marks omitted.) *Gibbons v. Bristol-Myers Squibb Co.*, supra, 919 F.3d 708. That is, "[a]s a general rule ... state law can hold a brand-name manufacturer liable for failing to use its powers under the CBE regulation to add a new warning to a drug label." *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 811 (7th Cir. 2018), cert. denied, 139 S. Ct. 2636 (2019). Conversely, if there is no newly acquired information, then the manufacturer has no authority to change its label and related state failure to warn claims are preempted. See *Utts v. Bristol-Myers Squib Co.*, 251 F. Supp.3d 644, 673 (S.D.N.Y. 2017) ("the plaintiffs' failure to warn claims are preempted because the information upon which the [plaintiff] relies to plausibly plead these claims does not, upon examination, demonstrate that any newly acquired information exists to support a label change pursuant to CBE regulations.")

The Code of Federal Regulations at 21 C.F.R. § 314.3 (b) defines "newly acquired information" as "[D]ata, analyses, or other information not previously submitted to the Agency, 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 FDA." 21 C.F.R. § 314.3(b). From this definition, it appears that the concept of "newly acquired information" has two components. The first refers to the quality or

reliability of the new information or what the Supreme Court referred to as the requirement that "reasonable evidence" exist. *Albrecht*, supra, 139 S. Ct. 1679. In edited form, the CBE regulation requires "[D]ata, analyses, or other information ... which may include (but is not limited to) data derived from ... clinical studies, reports of adverse events, or ... 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 ...." Further, the CBE regulation refers to 21 C.F.R. § 201.57 (c), which provides that "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is *reasonable evidence* of a causal association with a drug; a causal relationship need not have been definitely established." (Emphasis added.) 21 C.F.R. § 201.57 (c) (6) (i); see note 4 supra. The FDA has stated the following concerning the purpose of the reasonable evidence standard: "Expressly requiring that a CBE supplement reflect newly acquired information and be based on sufficient evidence of a causal association will help to ensure that scientifically accurate information appears in the approved labeling for such products." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,604, 2008 WL 3874230 (Aug. 22, 2008).

The second component of "newly acquired information" is its newness. It is only reasonable that "Newly acquired information" should be new. The regulation refers to newness on four occasions, which the court highlights in the following restatement of the definition: "[D]ata, analyses, or other information *not previously submitted to the Agency*, 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 FDA." (Emphasis added.) 21 C.F.R. § 314.3(b). As stated, in the absence of this sort of new information, a manufacturer would not have authority to amend its label under the CBE regulation and a claim under state law that it should have done so would face preemption. See *Utts v. Bristol-Myers Squib Co.,* supra, 251 F. Supp.3d 673.

There is, to be sure, a second basis for impossibility preemption in the drug labeling context. That basis arises if there is "clear evidence" that the FDA would not have approved a change to the drug label. In *Wyeth v. Levine,* 555 U.S. 555 (2009), the Supreme Court stated that "absent clear evidence that the FDA would not have approved a change to [the drug's] ... label, we will not conclude that it was impossible for [the manufacturer] ... to comply with both federal and state requirements." Id., 571. Ten years later, the *Albrecht* Court defined "clear evidence" to mean evidence showing that the drug manufacturer "fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." *Albrecht*, supra, 139 S. Ct. 1678.

Citing *Albrecht,* the plaintiff claims that in this context a "state law claim is preempted **only** when there is 'clear evidence' that the FDA would not have approved a change to the drug's label." (Emphasis in original) (Pl. Br., p. 14.) This statement, which the plaintiff and her lawyers have made repeatedly, is simply not correct.[5] The decisions of and within the Second Circuit, to

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[5]The plaintiff's lawyers are the lead counsel in the Consolidated Pradaxa Docket. See note 3 supra. The court has decided preemption issues in two other cases on the docket: *Roberto v. Boehringer Ingelheim Pharmaceuticals, Inc.* No. CPLHHDCV166068484S, 2019 WL 5068452, *9-*24 (Conn. Super. Ct. Sept. 11, 2019) (*Roberto*); and *Adkins v. Boehringer Ingelheim Pharmaceuticals,* No. X03HHD CV16-6065131S, 2020 WL 1890681 (Conn. Super. Ct. Mar. 13, 2020) (*Adkins*). In any case, although the plaintiff states that the *Albrecht* "clear evidence" test is the only path to preemption, the plaintiff's brief largely ignores her own

which Connecticut state courts afford "particularly persuasive weight" in the interpretation of federal statutes; *Webster Bank v. Oakley*, 265 Conn. 539, 555 n.16, 830 A.2d 139 (2003), cert. denied, 541 U.S. 903 (2004); make clear that the preemption test is two-pronged. Thus, in *Gibbons v. Bristol-Myers Squibb Co.*, supra, 919 F.3d 708, the Second Circuit stated: "to state a claim for failure-to-warn that is not preempted by the FDCA, a plaintiff must plead a labeling deficiency that [Defendants] could have corrected using the CBE regulation ....If the plaintiff meets that standard, the burden shifts to the party asserting a preemption defense to demonstrate that there is clear evidence that the FDA would not have approved a change to the [prescription drug's] label." (Citations omitted; internal quotation marks omitted.) While the present case does not involve a challenge to the complaint or to the plaintiff's pleading, *Gibbons* makes clear that the threshold issue is whether there is a "labeling deficiency that [Defendants] could have corrected using the CBE regulation ...." As discussed, that labeling correction can only take place if there is newly acquired information. At least three other courts within the Second Circuit have continued, after *Albrecht,* to apply a two-pronged test in which the manufacturer may establish preemption: "(1) by showing that it was prohibited by federal law from [unilaterally] modifying the FDA-approved labeling; or (2) by presenting clear evidence that the FDA would not have approved a change to the drug's label." (Internal quotation marks omitted.) *McGrath v. Bayer HealthCare Pharmaceuticals, Inc.*, 393 F. Supp.3d 161, 167 (E.D.N.Y. 2019). Accord *Gayle v. Pfizer, Inc.*, No. 19CV3451, 2020 WL 1685313, at *4 (S.D.N.Y. Apr. 7, 2020) (quoting *Gibbons*); *Sabol v. Bayer Healthcare Pharmaceuticals, Inc.*, 439 F. Supp.3d 131, 147 (S.D.N.Y. 2020) ("Bayer must (1) demonstrate that Sabol fails to allege facts showing that it could have

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statement and argues that there was newly acquired information.

unilaterally changed Magnevist's label under CBE, or (2) present clear evidence that the FDA would not have approved a change to the drug's label," citing *Wyeth v. Levine*, 555 U.S. 555, 568-73 (2009)). Our own Supreme Court has now cited the *Gibbons* preemption standard favorably. See *Boone v. Boehringer Ingelheim*, ___ Conn. ___, ___ n.33, ___ A.3d ___, No. 20200, 2020 WL 2121063, at *13 (Conn. May 4, 2020) ("The clear evidence standard in *Wyeth* applies only when a defendant seeks to prove that compliance with a state law obligation remains impossible *notwithstanding its ability to act unilaterally under federal law.*" [Emphasis in original.])

Neither *Wyeth* nor *Albrecht* is to the contrary. The *Wyeth* Court observed that the concept of "newly acquired information" became a part of the CBE regulation in 2008 and that "Wyeth could have revised Phenergan's label even in accordance with the amended regulation." *Wyeth v. Levine,* supra, 555 U.S. 568-71. It then added: "Of course, the FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications. But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements.... Wyeth has offered no such evidence." Id., 571-72.

Although the *Albrecht* Court did not specifically identify the test as being two-pronged, it nonetheless acknowledged the concept of "newly acquired information." *Albrecht*, supra, 139 S. Ct. 1673, 1679. The Court noted that Merck, the manufacturer of Fosamax, "conceded that the FDA's CBE regulation would have permitted Merck to try to change the label to add a warning before 2010, but Merck asserted that the FDA would have rejected that attempt." Id., 1675. It also "[assumed] ... that ... there is sufficient evidence to find that [the manufacturer] violated state

law by failing to add a warning about atypical femoral fractures to the Fosamax label." Id., 1678. Thus, although there was no need to address the newly acquired information prong any further in *Albrecht*, the absence of newly acquired information remains a basis for preemption in these cases generally.[6]

III

The court applies the accepted standards governing summary judgment motions. "Practice Book § [17-49] requires that judgment shall be rendered forthwith if the pleadings, affidavits and any other proof submitted show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law. A material fact is a fact that will make a difference in the result of the case.... The facts at issue are those alleged in the pleadings....

"In seeking summary judgment, it is the movant who has the burden of showing the nonexistence of any issue of fact. The courts are in entire agreement that the moving party for summary judgment has the burden of showing the absence of any genuine issue as to all the material facts, which, under applicable principles of substantive law, entitle him to a judgment as a matter of law. The courts hold the movant to a strict standard. To satisfy his burden the movant must make a showing that it is quite clear what the truth is, and that excludes any real doubt as to the existence of any genuine issue of material fact.... As the burden of proof is on the movant, the evidence must be viewed in the light most favorable to the opponent....

"The party opposing a motion for summary judgment must present evidence that

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[6]Contrary to the plaintiff's suggestion, preemption based on the absence of newly acquired information is not so much a matter of whether there is an "affirmative FDA decision" that directly prohibits a label change as it is whether the manufacturer has a basis to comply with the federal CBE regulation. If the manufacturer does not have such a basis, then preemption results from the force of the regulation rather than direct FDA action. (Pl. Br., p. 20.)

demonstrates the existence of some disputed factual issue.... The movant has the burden of showing the nonexistence of such issues but the evidence thus presented, if otherwise sufficient, is not rebutted by the bald statement that an issue of fact does exist.... To oppose a motion for summary judgment successfully, the nonmovant must recite specific facts ... which contradict those stated in the movant's affidavits and documents.... The opposing party to a motion for summary judgment must substantiate its adverse claim by showing that there is a genuine issue of material fact together with the evidence disclosing the existence of such an issue.... The existence of the genuine issue of material fact must be demonstrated by counteraffidavits and concrete evidence....' (Citations omitted; internal quotation marks omitted.) *Morrissey-Manter v. Saint Francis Hospital & Medical Center*, 166 Conn. App. 510, 517, 142 A.3d 363, cert. denied, 323 Conn. 924, 149 A.3d 962 (2016).

These rules apply generally to summary judgment motions based on affirmative defenses such as the defendant's preemption defense. See *Riley v. Pierson*, 126 Conn. App. 486, 490–92, 12 A.3d 581 (2011); *Petro, Inc. v. U.S. Coffee, Inc.*, No. FSTCV116009308S, 2014 WL 279655, at *1 (Conn. Super. Ct. Jan. 2, 2014). In particular, in a case of this nature, if the defendant makes an initial showing of entitlement to preemption, the burden shifts to the plaintiff to identify with some specificity any newly acquired information that purportedly could have justified a CBE label change. The defendant retains the ultimate burden of proof. See *Roberto*, supra, 2019 WL 5068452, at *11 n.19.

The *Albrecht* Court held with respect to the second, "clear evidence" prong of the analysis that the "question is a legal one for the judge, not a jury." *Albrecht*, supra, 139 S. Ct. 1679. See also id., 1672 ("We here determine that this question of pre-emption is one for a judge to decide,

not a jury.") The Court reasoned that "judges are better suited than are juries to understand and to interpret agency decisions in light of the governing statutory and regulatory context." Id., 1680. The Court added that "sometimes contested brute facts will prove relevant to a court's legal determination about the meaning and effect of an agency decision." Id. The Court observed: "[W]e consider these factual questions to be subsumed within an already tightly circumscribed legal analysis. And we do not believe that they warrant submission alone or together with the larger pre-emption question to a jury. Rather, in 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." (Internal quotation marks omitted.) Id.

Although the issues and analysis on the first prong of the preemption test, involving newly acquired information, are not identical to those involved in the second, clear evidence prong, it seems unlikely that the Supreme Court would hold that the first prong is triable to the jury while the second prong is not. Both prongs involve complicated legal analysis. The question of whether there is newly acquired information seems ill-suited for a jury. Accordingly, the court has ruled that both the legal issues and any "subsidiary factual questions" in deciding whether there is newly acquired information are matters for a court, not a jury, to decide. (Internal quotation marks omitted.) Id. See *Roberto,* supra, 2019 WL 5068452, *12. See also *Ridings v. Maurice,* No. 4:15-cv-00020-JYM, slip op. at 3 (W.D. Mo. Oct. 20, 2019) ("Consistent with *Albrecht*, the Court will be the factfinder on the question of whether Boehringer's affirmative defense of preemption can be established so as to bar Ridings' state law failure-to-warn claims."

[footnote deleted]).[7]

IV

A

In *Roberto*, the court addressed the defendant's similar argument that federal preemption barred the plaintiff's state law claim that the Pradaxa label failed to warn adequately about the elevated risk of bleeding in patients with a preexisting history of GERD. The court observed that the language in the U.S. label "discloses that GERD is a possible adverse reaction of taking Pradaxa [but] ... not ... the almost opposite proposition that, in patients with a history of GERD, bleeding is a possible adverse reaction of taking Pradaxa."[8] The court found, in contrast, that the 2011-13 European label for Pradaxa, which is entitled "Summary of Product Characteristics" and

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[7]Thus, the plaintiff's suggestion in her brief and its conclusion that the court should deny summary judgment because there are "material issues of fact" makes little sense in view of their simultaneous acknowledgment that the issue is generally one for the court to decide, not a jury. (Pl. Br., pp. 14 & n.39, 35.) The defendants should not lose their preemption defense merely because the plaintiff generates a factual dispute. Such a result would lead to the wrong outcome in situations in which the plaintiff's evidence is incorrect or not credible. Rather, there should be a forum for resolving the factual dispute. If it is not the jury, as the plaintiff acknowledges, then it must be the court, as *Albrecht* states. For example, a factual dispute about whether a document was "previously submitted to the FDA" for purposes of determining whether there is newly acquired information is precisely the type of "subsidiary factual question" that the court could and should resolve, perhaps at an evidentiary hearing. The plaintiff's contrary approach would essentially mean that summary judgment would enter for the plaintiff on the special defense of preemption even though she has not moved for summary judgment and there are outstanding fact issues in need of resolution. There is no basis for such a one-sided approach.

In this case, however, the court does not find any material disputes of fact and is capable of resolving the matter on the papers.

[8]Section 6.1 of the original label stated: "Patients on PRADAXA 150 mg had an increased incidence of gastrointestinal reactions (35% vs. 24% on warfarin). These were commonly dyspepsia ... and gastritis-like symptoms (including GERD ....)." Similarly, § 17.3 of the original label is entitled "Gastrointestinal Adverse Reactions" and instructs doctors to have their patients "call their health care provider if they experience any signs or symptoms of dyspepsia or gastritis: ... epigastric discomfort, GERD (gastric indigestion)." (Def. Ex. 2.)

abbreviated as "SmPC" conveys a "clear message based on data that, for patients with a history of GERD, there is an 'elevated risk of major gastrointestinal bleeding' .... [and that] the European label contains information about GERD that meets a threshold level of reliability and detail." The court also found that "the record in this case of whether the defendants submitted the European label to the FDA prior to the plaintiff's bleed is unclear." Accordingly, the court concluded that the statements in the European label about GERD qualified as newly acquired information and that federal law did not preempt the plaintiff's state law claims. *Roberto,* supra, 2019 WL 5068452, at *21-*24.

The parties have now presented an expanded record that calls for further discussion of the *Roberto* findings. As stated earlier, the first issue in determining whether newly acquired information exists is whether there is "reasonable evidence" of a risk of either a "different type" or of "greater ... frequency" than what the U.S. label discloses. The plaintiff renews the argument that the European Pradaxa label, which is Plaintiff's Exhibit 80 here, constitutes a vital component of the newly acquired information in this context. As stated in *Roberto*, "Exhibit 80 states a '[d]ate of first authorisation [sic]' as August 1, 2011 and a 'date of latest renewal' of January 17, 2013, both of which fall within the relevant time period between October, 2010, when the FDA first approved Pradaxa, and ... when the plaintiff suffered [her] ... bleed. Page 60 of the European label contains the following statement: 'For subjects with gastritis, esophagitis, or gastroesophageal reflux the dose of 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastrointestinal bleeding ....' Page 63 states: 'This increased risk [of major gastrointestinal bleeding] was seen in ... the presence of ...

gastroesophageal reflux ...."[9] Page 64 contains a chart that summarizes 'factors which may increase haemorrhagic risk.' In the category of 'Diseases/procedures with special haemorrhagic risks' the following are listed: 'Esophagitis, gastritis or gastroesophageal reflux.' The label adds on page 64 that '[t]he presence of ... conditions ... which significantly increase the risk of major bleeding requires a careful benefit-risk assessment.'" *Roberto*, supra, 2019 WL 5068452, at *21 (citing Ex. 30.)

The plaintiff now presents additional evidence. A peer-reviewed article in a 2013 medical journal states: "Patients with pre-existing dyspepsia or gastroesophageal reflux disease may benefit from avoiding dabigatran."[10] (Pl. Ex. I (J.S. Kalus, "Antithrombotic alternatives for stroke prevention in atrial fibrillation: critical differences and remaining questions," Drugs in Context, p. 5 (2013))). In a 2014 article that sought to "identify the reasons and risk factors for discontinuation of [dabigatran] therapy" in certain populations, the authors reported: "some patients might have had pre-existent upper gastrointestinal pathology that required treatment with a proton pump inhibitor and H2-receptor blocker, and that was subsequently exacerbated by

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[9]The complete paragraph provides as follows: "In a study of prevention of stroke and SEE [systemic embolic events] in adult patients with NVAF [nonvalvular atrial fibrillation], dabigatran etexilate [Pradaxa] was associated with higher rates of major gastrointestinal (GI) bleeding which was statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux requiring increase the risk of GI bleeding. In these atrial fibrillation patients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered and posology recommendations in section 4.2 be followed. The administration of a PPI can be considered to prevent GI bleeding." (Pl. Ex. 80, p. 63.) It is apparent that the third sentence contains a grammatical error centering around the word "requiring." In the text above, the court has attempted to quote an excerpt from this paragraph that fairly states its intended meaning.

[10]Dabigatran is the chemical name for Pradaxa.

dabigatran." (Pl. Ex. K (M.H. Ho, et al., "Continuation of Dabigatran Therapy in 'Real-World' Practice in Hong Kong," PLOS/One, pp. 1, 6 (Aug., 2014))).[11]

The defendants challenge this evidence. The court recognizes that the information in the European label does not constitute a lengthy analysis and primarily serves to satisfy European labeling requirements, which have led to a Pradaxa label that consumes 162 pages. (Pl. Ex. 80.) See also *Ridings v. Maurice*, No. 15-00020-CV-W-JTM, 2020 WL 1264178, at *17 (W.D. Mo. Mar. 16, 2020), quoting *McDowell v. Eli Lilly & Co.*, 2015 WL 845720, op. at *5 (S.D.N.Y. Feb. 26, 2015) ("[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.") On the other hand, the fact that the information in the European label ultimately comes from the defendant makes it hard for the defendant to deny the information's reliability.

It is also true, as the defendants point out, that the quotations from articles cited by the

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[11]The plaintiff also cites a 2019 article by Chan and Eikelboom. (Pl. Ex. J). However, studies published after the plaintiff's injury in the case would not constitute or contribute to newly acquired information. See *McGrath v. Bayer HealthCare Pharmaceuticals Inc.*, supra, 393 F. Supp.3d 166. The plaintiff's quotation from a 2011 article by Eikelboom is more relevant temporally: "The prevalence of gastrointestinal tract pathology, such as diverticulosis and angiodysplasia, increases with age, and the risk of bleeding from affected areas might be increased by direct exposure to dabigatran." (Pl. Ex. 3124 (J.W. Eikelboom, et al., "Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation," Circulation, p. 2370 (Mar. 2011))). However, the passage is unclear as to whether it refers to patients with GERD. The plaintiff also claims support from a 2013 article by Bytzer and an adverse event report, but the plaintiff's brief neither quotes from them nor provides page cites. (Pl. Exs. 1651, 3330.) The court therefore cannot verify the plaintiff's point in this regard. See also *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 44 (2011) ("[t]he fact that a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event.")

plaintiff are not necessarily conclusive or even pertinent.[12] But, to the extent relevant, these quotations at least mean that this case is not based solely on foreign labeling. Cf. *Ridings v. Maurice*, supra, 2020 WL 1264178, at *17 ("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." [Emphasis added.]) Ultimately, the CBE regulations provide that "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is *reasonable evidence* of a causal association with a drug; a causal relationship need not have been definitely established." (Emphasis added.) 21 C.F.R. § 201.57 (c) (6) (i); see note 4 supra. Applying these standards, and viewing the plaintiff's evidence cumulatively, the court concludes that there was "reasonable evidence" of a different or greater risk, not stated in the U.S. label, of bleeding in patients with GERD sufficient to satisfy CBE standards.

B

The more difficult question concerns the second component of "newly acquired information," which addresses its newness. As stated, the definition of "newly acquired information" twice uses the term "new" and also uses the phrases "not previously submitted to the Agency," and "previously included in submissions to FDA."

In *Roberto* and *Adkins*, the court followed the existing case law on this issue, as well as what appears to be the plain language of the regulation, and concluded that BI's submissions to the FDA concerning Pradaxa blood plasma concentrations and the usefulness of blood monitoring

[12]The Kalus article does not identify a reason, and specifically does not identify bleeding as the reason, why it recommends against the use of Pradaxa in patients with preexistent GERD. In the Ho article, dyspepsia, rather than bleeding, was the most common cause for discontinuation of Pradaxa and it is not clear that patients who "required treatment with a proton pump inhibitor and H2-receptor blocker" had GERD. (Pl. Ex. K, pp. 4, 6.)

satisfied the "previously submitted to the Agency" component. See note 5 supra. See also *Dolin v. GlaxoSmithKline LLC*, supra, 901 F.3d 816 ("The [2011] article contained the same figures as GSK's 2005 analysis, which GSK submitted to the FDA. There is no basis to conclude that this was a new analysis or that it was 'not previously submitted to the Agency.'")); *In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Product Liability Litigation*, 185 F. Supp.3d 761, 769 (D.S.C. 2016) ("any claim that a drug label should be changed based on information previously submitted to the FDA is preempted because the CBE regulation cannot be used to make a label change based on such information.") Since this court's decision in *Roberto* and *Adkins*, other federal courts have at least recognized the newness component of the newly acquired information regulation. See *Stube v. Pfizer Inc.*, No. 6:19-CV-6087, 2020 WL 1249909, at *8 (W.D. Ark. Mar. 16, 2020) ("Plaintiffs alleged that none of the above information had been previously disclosed to the FDA."); *Ridings v. Maurice*, supra, 2020 WL 1264178, at *16 ("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 *Roberto,* as mentioned, the court also concluded that the record was unclear whether BI had previously submitted the GERD information in the European label at issue here. *Roberto*, supra, 2019 WL 5068452, *21-24.

None of these cases went into detail on the meaning of the phrase "previously submitted to the Agency." The present case requires the court to do so. The question raised is whether, as a

legal matter, straightforward submission of information to the FDA that is equivalent to the claimed newly acquired scientific evidence, without additional action such as a request for a label change or an FDA response, satisfies the regulatory standard. The court will then address whether, as a factual matter, the defendants submitted the same or equivalent information to the FDA in this case.

1

The defendants advocate for a "straightforward submission" approach in which submission or transmission, without more, of the data or information equivalent to the plaintiff's new information satisfies the "previously submitted to the Agency" prong. The plaintiff appears to contend that the information submitted to the FDA must be "tethered to a proposed label change" in order to qualify as "previously submitted to the Agency." (Pl. Br., p. 28.)[13]

To resolve this conflict and interpret the regulation correctly, the court should apply the rules of statutory construction. See *Morales v. Sociedad Espanola de Auxilio Mutuo y Beneficencia*, 524 F.3d 54, 59 (1st Cir. 2008), cert. denied, 555 U.S. 1097 (2009). "[W]e begin our analysis by examining the plain language of the text of the regulation, giving the words their ordinary meaning .... If the meaning of the text is clear, our endeavor is at an end, and we must enforce the regulation in accordance with its plain meaning." *Board of Education of Gallup-McKinley County School v. Native American Disability Law Center, Inc.*, 959 F.3d 1011, 1013 (10th Cir. 2020). Whenever possible, courts should interpret a federal regulation so that no clause, sentence, or word is superfluous, void, or insignificant. See *Morales v. Sociedad*

[13]It is difficult to determine the plaintiff's position for certain because the plaintiff's brief does not discuss, or even quote, the full regulatory definition of "newly acquired information" found in 21 C.F.R. § 314.3 (b).

Espanola de Auxilio Mutuo y Beneficencia, supra, 59; *Contreras v. Astrue*, No. CIV 08-1196 DWF/JJK, 2009 WL 5252828, at *10 (D. Minn. Aug. 26, 2009) (citing *TRW Inc. v. Andrews*, 534 U.S. 19, 31 (2001)). See also *Newman v. Planning & Zoning Commission*, 293 Conn. 209, 214, 976 A.2d 698 (2009) ("Whenever possible, the language of zoning regulations will be construed so that no clause is deemed superfluous, void or insignificant." [Internal quotation marks omitted.])

Application of these rules leads directly to the conclusion that straightforward submission is sufficient. The plain language of the regulation provides, again, that newly acquired information consists of "[D]ata, analyses, or other information *not previously submitted to the Agency*, 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 FDA.*" (Emphasis added.) 21 C.F.R. § 314.3 (b). There is no requirement in the regulatory language that the submission be tethered to a label change request or even that the FDA officially acknowledge the submission.[14]

Without detracting from the significance of the rule's plain language, it is useful to

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[14]The plaintiff's apparent position that the unadorned phrase "previously submitted to the Agency" equates to the *Albrecht* "clear evidence" standard – that the manufacturer "fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning"; *Albrecht*, supra, 139 S. Ct. 1678 – involves wholesale rewriting of the regulation, an executive or legislative branch task in which the court cannot engage. The two preemption stages remain separate. Even if the manufacturer is not preempted under the CBE regulation because it has not previously submitted newly acquired information to the FDA, it can acquire the benefit of preemption if it later submits the material to the FDA in a manner that satisfies the clear evidence test.

examine the history of the rule. The FDA has had a codified CBE rule since approximately 1985. In January, 2008, the FDA proposed amending its CBE regulations to incorporate the concept of "newly acquired information." In its comments concerning the proposed rule, the FDA explained that the FDCA "requires new drugs ... to be approved by the FDA prior to their distribution in interstate commerce .... Allowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress. Indeed, permitting a sponsor to unilaterally rewrite the labeling for a product following FDA's approval of a product and its labeling would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated." Accordingly, the FDA stated that "[t]he CBE supplement procedures are a *narrow exception* to this general rule." (Emphasis added.) Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2849-50, 2008 WL 136335 (January 16, 2008) (Jan. 2008 Supplemental Applications).[15]

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[15]The plaintiff objected at oral argument to reliance on FDA comments on its proposed rule on the ground that the Supreme Court in *Wyeth* counseled against doing so. In *Wyeth*, the Court addressed a statement in the preamble to a 2006 FDA regulation in which the FDA declared that the "FDCA establishes both a floor and a ceiling, so that FDA approval of labeling ... preempts conflicting or contrary State law." (Internal quotation marks omitted.) *Wyeth v. Levine*, supra, 555 U.S. 575. The Court declined to give deference to these comments because it had "not deferred to an agency's *conclusion* that state law is pre-empted." (Emphasis in original.) Id. It explained, however, that "[w]hile agencies have no special authority to pronounce on pre-emption absent delegation by Congress, they do have a unique understanding of the statutes they administer and an attendant ability to make informed determinations about how state requirements may pose an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." (Internal quotation marks omitted.) Id., 576–77. In the present case, the FDA statements quoted by the court are not conclusions of law as in *Wyeth*. Rather, they are statements about an agency's experience in administering its own rules, its reasons for proposing amendments and, later in the text, the agency's own regulatory process. There is nothing in *Wyeth* that precludes reliance on such statements. Indeed, there is perhaps no better source for this information than the agency itself.

The FDA then addressed the "previously submitted" component of the rule. The agency stated that "if a postmarket study demonstrates that an approved product has a more severe risk of a significant adverse reaction than previously known, a CBE supplement may be appropriate. However, if a postmarket study provides data about a product that is cumulative of information previously submitted to FDA, a CBE supplement would not be appropriate. Similarly, if a sponsor receives reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, such information may be considered newly acquired information that could form the basis for an appropriate CBE supplement. However, if the reports of adverse events are consistent in type, severity, and frequency with information previously provided to FDA, such reports may not constitute newly acquired information appropriate for a CBE supplement." Id., 2850. Ultimately, the agency addressed the purpose of the "previously submitted" language: "Allowing a sponsor, without prior FDA approval, to add information to the labeling for a product based solely on data previously submitted to the FDA would undermine FDA's approval process and could result in *unnecessary or confusing information* being placed in the labeling for a drug, biologic, or medical device." (Emphasis added.) Id., 2851. See also id. ("labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance.") Thus, the "previously submitted" component of the rule serves to preserve the very integrity of the FDA approval process and ensure that physicians and patients receive information about a drug in a meaningful way.[16]

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[16]The comments on the final rule in August, 2008 reveal an exception to or qualification of the "previously submitted" component. One commentator "requested that FDA clarify the temporal relationship between the submission of new information to FDA and a subsequent CBE

At oral argument, the plaintiff contended that, when, as here, the FDA makes no response to the prior data submission, a conclusion that the FDA has actually read the submission constitutes nothing more than a presumption, which would run contrary to the presumption against preemption. See *Wyeth v. Levine*, supra, 555 U.S. 565 n.3. It is true that, in this case, as will be seen, the defendants rely upon a sentence or two or, at most, an entry in a scientific table found in documents submitted to the FDA that run from 100 to 600 pages long in order to show that they previously submitted the relevant GERD-related bleed risk information to the FDA. The FDA made no specific response to these submissions.[17]

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supplement." In response, the FDA stated: "FDA agrees that this issue should be clarified here so as to provide greater guidance to sponsors in determining their regulatory obligations. Newly acquired information includes information not previously submitted to FDA. If a sponsor submits data or analysis to FDA as part of a discussion of the kind of labeling change that would be appropriate and decides as a result of that discussion to prepare and submit a CBE supplement, then the supporting data or analysis will not be considered 'previously submitted to FDA'—even if it was not first submitted on the same day as the CBE supplement. This allows for a labeling change when a sponsor submits data or analysis to FDA before the sponsor has completed its CBE supplement, and is also designed so as not to deter the sponsor from submitting the information *for fear that such a submission would preclude the sponsor from making a CBE change.* This clarification is designed to address the situation where a sponsor submits data or analyses to FDA as part of the process of determining what labeling change is appropriate, and then diligently and promptly prepares a CBE supplement." (Emphasis added.) Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 FR 49607, 2008 WL 3874230 (Aug. 22, 2008). Thus, information submitted in conjunction with a CBE notification would not constitute information "previously submitted" to the FDA. At the same time, this discussion confirms that, ordinarily, prior submission of the data in question "would preclude the sponsor from making a CBE change." Id.

[17]The defendants cite two FDA reviews for the proposition that "BI and the FDA have also engaged in extensive discussions regarding Pradaxa's GI bleeding profile and GI adverse events." Upon examination, however, neither review specifically mentions the increased risk of bleeding in patients with a history or diagnosis of GERD. (Def. Br., p. 10 n.10 (citing Def. Exs. 19, 20.))

The initial response is that the plain language of the rule does not require FDA acknowledgment of a company's documentary submissions. More broadly, however, the FDA has explained that it does consider all material submitted. In the Federal Register comments concerning its proposed newly acquired information rule, the FDA stated the following: " Before approving an NDA [new drug application], BLA, or PMA, *FDA undertakes a detailed review of the proposed labeling*, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling. Under the [FDCA] ... , the Public Health Service Act (the PHS Act), and FDA regulations, the agency makes approval decisions, including the approval of supplemental applications, *based on a comprehensive scientific evaluation of the product's risks and benefits* under the conditions of use prescribed, recommended, or suggested in the labeling .... *FDA's comprehensive review* is embodied in the labeling for the product which reflects *thorough FDA review* of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively .... Moreover, after approval, FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate" (Emphasis added; Internal citations omitted.) Jan. 2008 Supplemental Applications, supra, 73 Fed. Reg. 2851, 2008 WL 136335. The FDA made substantial similar comments at the time of the final rule. See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 FR 49604, 2008 WL 3874230 (Aug. 22, 2008). These comments make clear that the FDA considers the material submitted and that the label itself is the clearest expression of FDA's views and concerns.

The plaintiff also expresses concern about a "data dump" and a "paper blizzard." (Pl. Br., pp. 5, 32-33.) There is no evidence or indication, however, that the defendants submitted information about GERD to the FDA for the purpose of preempting state law suits. Indeed, such a suggestion requires a vivid imagination, as there were no cases from 2010 to 2012, when the defendants submitted the data in question, that had related the "previously submitted to the Agency" language in § 314.3 (b) to the issue of preemption. From all appearances, the defendants submitted the data in question to comply with reporting requirements or to assist the FDA.

At oral argument, the plaintiff claimed that the Third Circuit's decision in *In re Avandia Marketing, Sales and Products Liability Litigation* (*Avandia*), 945 F.3d 749 (3d Cir. 2019), held that a data submission must be "tethered" to an unsuccessful request for a label change in order to have a preemptive effect. Of course, § 314.3 (b) does not say that. But neither did *Avandia.* The *Avandia* Court initially discussed the second "clear evidence" preemption test and concluded that "the upshot of [*Albrecht*]... is that a drug manufacturer must show that the FDA made a fully informed decision to reject a change to a drug's label in order to establish the 'demanding defense' of impossibility preemption ..... If the question of whether the FDA was 'fully informed' was not tethered in time to the question of whether the FDA indeed rejected the proposed warning, the 'fully informed' prong of the test espoused in [*Albrecht*] ... would be rendered superfluous." *Avandia,* supra, 759.

The *Avandia* Court then turned to the newly acquired evidence test. The Court focused on whether there was sufficient evidence of new information and rejected the company's arguments that it did not have the newly acquired information necessary to make a labeling change under the CBE process prior to mid-2006. The Court found that, "at the very least, it appears that GSK [the

company] could have used the CBE process to add an ischemic-risk warning as early as August 2005 ...." Id., 760. In a footnote, the Court added that it took "no position with respect to whether GSK could have used the CBE process, or otherwise sought to change Avandia's label, to add an ischemic-risk warning prior to August 2005." Id., 760 n. 2. At no point did the Court quote § 314.3 (b) or discuss the "previously submitted" prong of the newly acquired information preemption category. *Avandia* simply did not address the issue raised in the present case.

As stated above, the cases that have addressed the issue have generally held that prior submission of the data in question precludes use of the CBE process and gives rise to a preemption defense. See *Dolin v. GlaxoSmithKline LLC*, supra, 901 F.3d 816; *Ridings v. Maurice*, supra, 2020 WL 1264178; *In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Product Liability Litigation*, supra, 185 F. Supp.3d 769. As the court has now explained, this result is consistent with both the plain language and the purpose of the rule.

2

The remaining issue is whether, prior to the plaintiff's bleed, the defendants submitted information to the FDA that was equivalent to the claimed newly acquired information. Such information, as now explained, would satisfy the "previously submitted to the Agency" component of the rule, preclude use of the CBE process, and give rise to a preemption defense.

The defendants have met this standard. The defendants have produced evidence showing that, prior to Pradaxa's original approval in October, 2010, they submitted several reports to the FDA stating and demonstrating in tables that gastritis-like symptoms, defined to include GERD, in Pradaxa recipients "were associated with an increased risk of a major GI bleed by 3- to 4-fold and any bleed by 2- to 3-fold for all treatments ...." (Def. Ex. 3 at 141, 144 (BI Advisory

Committee Briefing Document, Aug. 27, 2010, citing Table 7.4.5: 2 ("Subjects with GI Bleeding Events for Subjects with Symptoms of Dyspepsia or Gastritis – RE-LY Study"))); Def. Ex. 6 at 213-14, 216 (BI Clinical Trial Report, Oct. 16, 2009 ("Gastritis-like symptoms increased the probability of a major GI bleed by 3 to 4-fold and any bleed by 2 to 3 fold for all treatments"), citing Table 12.2.3.2: 4 ("Number (%) of subjects with GI bleeding events for subjects with symptoms of dyspepsia or gastritis (safety set)")); Def. Ex. 7 at 107-08 (BI Summary of Clinical Safety, Nov. 4, 2009 ("Gastritis-like symptoms increased the probability of a major GI bleed by 3 to 4-fold and any bleed by 2 to 3 fold for all treatments"), citing Table 2.1.2.2 ("Frequency of subjects with dyspepsia and gastritis-like symptoms in Trial 1160.26 (safety set)" [footnote omitted].)) See also Def. Ex. 8 at 68 (BI Clinical Overview, Nov. 10, 2009) ("the adverse event of 'gastritis-like symptoms' ... was associated with a 2-3 fold higher rate of GI bleed regardless of treatment."); (Def. Br., pp. 3-4 & nn. 3, 4.) (citing testimony confirming that BI submitted these reports to the FDA.) These submissions to the FDA prior to the initial approval of the Pradaxa label are particularly important because, as stated, "FDA's comprehensive review is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." Jan. 2008 Supplemental Applications, supra, 73 Fed. Reg. 2851, 2008 WL 136335.

In addition, in September, 2012, after Pradaxa's approval but before a label change in December, 2013 and before the plaintiff's February, 2015 bleed, the defendants submitted to the FDA the very same SmPC or European label with the very same GERD bleed risk findings that the plaintiff relies upon here. (Def. Exs. 10, 11 at 50, 51, 54-55.) See also *Roberto*, supra, 2019

WL 5068452, at *14 (the 2013 label). Also during this time period, the defendants regularly submitted Periodic Safety Update Reports (PSURs) to the FDA, reporting that "[t]he SmPC states in section 4.4, Special Warnings and precautions for use, that ... the presence of gastroesophogeal reflux [increases] the risk of GI hemorrhages." (Def. Ex. 12, p. 282; Def. Ex. 13, p. 178; Def. Ex. 14, p. 163; Def. Ex. 15, p. 142.)

The plaintiff objects on the ground that the European label warns about "pre-existing" GERD whereas the materials that the defendants submitted to the FDA, except for the label itself, address "treatment emergent" GERD." (Pl. Br., p. 3.) However, the European label neither uses those terms nor refers to that distinction in any other way.[18] Further, neither side presents any evidence to show whether there is a different bleed risk based on the timing of when GERD develops. In any event, irrespective of how one characterizes the European label, the fact remains that the defendants submitted the very same material to the FDA. Thus, the court cannot exclude the materials submitted by the defendant to the FDA from the category of "previously submitted" on the ground that they address a different issue than the plaintiff's new information.[19] Therefore, the defendants could not have made a CBE label change concerning GERD and are entitled to preemption on the plaintiff's state law claims concerning the lack of additional GERD warnings in

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[18]The plaintiff observes that the court in *Roberto* summarized the European label as providing that, "for patients with a history of GERD, there is an 'elevated risk of major gastrointestinal bleeding.'" (Pl. Br., p. 4 (quoting *Roberto,* supra, No. 2019 WL 5068452, at *22.)) The court realizes that its language was imprecise, largely because there was no issue of preexisting versus treatment-emergent GERD at the time. Again, however, the European label does not make this distinction.

[19]Although the Kalus and Ho articles offered by the plaintiff do refer to "pre-existent" GERD, they do not contrast that condition with "treatment-emergent" GERD or any similar condition.

the Pradaxa label.

V

For the foregoing reasons, the court grants the defendants' motion for summary judgment.

It is so ordered.

414999
Carl J. Schuman
Judge, Superior Court

- Notice sent 8/25/20;
- Copy mailed OCR 8/25/20;