UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

CHARLIE UTTS and CIARA UTTS, Plaintiffs, -v- BRISTOL-MYERS SQUIBB COMPANY and PFIZER INC., Defendants.	16cv5668(DLC) OPINION AND ORDER

APPEARANCES:

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DENISE COTE, District Judge:

Plaintiffs Charlie and Ciara Utts bring this product liability lawsuit against defendants Bristol-Myers Squibb Company ("BMS") and Pfizer Inc. ("Pfizer"), alleging that Mr. Utts suffered severe gastrointestinal bleeding from taking Eliquis, a prescription drug manufactured, marketed, and

distributed by the defendants. They assert that the label did not adequately warn of the risk of excessive bleeding.

The defendants have moved to dismiss the Second Amended Complaint ("SAC") pursuant to Federal Rules of Civil Procedure 12(b)(6) and 9(b). The primary issues in this motion to dismiss are whether the plaintiffs' state law failure to warn claims are preempted by federal law and whether the label is adequate as a matter of law. For the following reasons, the defendants' motion is granted in its entirety.

Before describing each of the SAC's claims and addressing the legal challenges to them brought through this motion to dismiss, it is useful to provide an overview of the analysis that follows. Although the focus of the SAC is on an alleged failure by the defendants to warn that use of Eliquis, which belongs to a new class of blood thinners, runs the risk of causing excessive bleeding and has no known antidote, those allegations are largely abandoned in opposition to the motion to dismiss. The reason for this choice is not hard to discern. The risk of excessive bleeding from this blood thinner and the lack of an antidote were clearly disclosed to the Food & Drug Administration ("FDA") when it approved the drug, and are prominently disclosed to medical practitioners and patients on the FDA-approved labeling for the drug.

In opposition to this motion, therefore, the plaintiffs

emphasize two other, albeit related, issues with the drug. The plaintiffs emphasize in their brief that, despite the fact that there is a risk of excessive bleeding and no known antidote for the drug, the dosage recommendations for the drug are not individually tailored and the defendants do not recommend constant monitoring of patients using the drug. These claims fare no better.

When the SAC's allegations about dosage and monitoring are examined, those allegations fail as well. For instance, the SAC does not identify any specific warnings or guidance that should have been included on the label regarding either dosage or monitoring but were not. The plaintiffs have not identified any research or other clinical work that recommends another dosage strategy than that currently described on the label, or explains what specialized monitoring of a patient would accomplish. These two complaints concern features of the design of the drug that were well known to the FDA when it approved the drug.[1]

Faced with the fact that, as of today, there is no research or clinical experience to suggest that any changes to the Eliquis label's disclosures related to a risk of excessive

[1] The new class of drugs to which Eliquis belongs was designed to improve on the performance of predecessor blood thinners, in particular warfarin, in several ways, including by eliminating the need for meticulous dose adjustment.

bleeding are warranted, the plaintiffs argue vehemently that the motion to dismiss should be denied and that they should be permitted to conduct discovery to try to locate evidence in the defendants' files that might support their failure to warn claims. They emphasize that there is substantial ongoing litigation over the earlier drugs in the class of drugs to which Eliquis belongs. But, the ability of other plaintiffs in other litigation over other drugs to survive a motion to dismiss does not relieve the plaintiffs of the requirements imposed by Rule 12(b). Accordingly, the claims in the SAC, which reduced to their essence are attacks on the design of this drug, will be dismissed.

BACKGROUND

The facts are construed in favor of the plaintiffs. See Keiler v. Harlequin Enters. Ltd., 751 F.3d 64, 68 (2d Cir. 2014). Plaintiffs Charlie and Ciara Utts are both residents of California. Mr. Utts was diagnosed with atrial fibrillation[2] and prescribed Eliquis by his doctor. After taking Eliquis, Mr. Utts suffered severe gastrointestinal bleeding and was

[2] Atrial fibrillation is a common arrhythmia (i.e., abnormal heart beat) that can cause blood clots to form in the heart. Individuals with atrial fibrillation are at a high risk of stroke and use blood thinners such as Eliquis to reduce the risk of stroke.

hospitalized in July 2014 for approximately three weeks to undergo blood transfusions and several rounds of dialysis.

Eliquis -- the brand name of the prescription medicine apixaban[3] -- is a blood-thinning medication used to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Eliquis belongs to a class of drugs known as novel oral anticoagulants ("NOACs"). It does not have a known antidote or reversal agent. Unlike anticoagulant medications such as warfarin,[4] NOACs, including Eliquis, do not require periodic blood testing or impose dietary restrictions on users.

[3] The names "Eliquis" and "apixaban" are used interchangeably in this Opinion.

[4] Warfarin, like the NOACs, is a prescription anticoagulant, or blood thinner. Warfarin works by inhibiting vitamin K dependent clotting factors. Patients taking warfarin must be monitored every few weeks. The clotting test used to measure the amount of time it takes for a patient's blood to clot is called the prothrombin time ("PT") test. The results of the PT test are used to measure the INR, or International Normalized Ratio. A high INR indicates a high risk of uncontrollable bleeding, while a low INR indicates a high risk of blood clots. Regular measurement of INR levels is an essential component in the management of patients receiving warfarin treatment. Unlike Eliquis, warfarin has an antidote: vitamin K. Because of the antidotal effect of vitamin K, however, patients taking warfarin must follow a strict diet and limit their consumption of vitamin K-rich foods. Coumadin is one of the brand names for warfarin.

I. FDA Approval of Eliquis

The FDA approved Eliquis for sale and marketing in the United States in 2012.[5] Pursuant to federal law, all applications for FDA approval of new drugs must include a description of the clinical investigations of the drug, including an analysis of each clinical pharmacology study of the drug and each controlled clinical study pertinent to a proposed use of the drug. See 21 C.F.R. § 314.50(d)(5). In accordance with this requirement, the defendants submitted the results of the international clinical trials known as ARISTOTLE. The plaintiffs allege that the defendants' agents "committed fraud in their conduct of the ARISTOTLE study," by, amongst other things, "concealing side effects which occurred in test users of Eliquis."[6]

While the defendants' application was pending before the FDA, Dr. Thomas Marcinak, an FDA employee appointed to review

[5] Eliquis is one of four NOACs to receive FDA approval. Pradaxa (generic name "dabigatran"), Xarelto (generic name "rivaroxaban"), and Savaysa (generic name "edoxaban") received FDA approval in 2010, 2011, and 2015, respectively. This Opinion uses the NOACs' generic and brand names interchangeably.

[6] The SAC also alleges the following deficiencies with the ARISTOTLE study: (1) an unreported death; (2) loss of subjects to follow-up; (3) major dispensing errors, such as indicating that certain subjects were receiving Eliquis when they were not; (4) poor overall quality control; and (5) changing and falsifying records, including records disappearing just before the FDA conducted a site visit.

the Eliquis application, recommended that the proposed Eliquis label discuss the quality control problems associated with the ARISTOTLE study. In response to concerns about the rigor of the ARISTOTLE study, the defendants stated that they were submitting additional data to the FDA for its consideration.

II. The Eliquis Label

At the time Mr. Utts was prescribed Eliquis, the label[7] contained several warnings about the risk of bleeding and the lack of an effective antidote. The label also offered specific

[7] The term "label" is defined as "a display of written, printed, or graphic matter upon the immediate container of any article." 21 U.S.C. § 321(k). The term "labeling" means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Id. § 321(m). All labeling must be approved by the FDA. Id. § 355(b)(1)(F). Specific "patient labeling" -- also referred to as a "medication guide" -- is required where the FDA determines that one or more of the following circumstances exists: (1) the drug product is one for which patient labeling could help prevent serious adverse effects; (2) the drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or to continue to use, the product; and (3) the drug product is important to health and patient adherence to direction for use is crucial to the drug's effectiveness. 21 C.F.R. § 208.1(c). The purpose of patient labeling is "to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products." Id. § 208.1(b). Accordingly, medication guides must be written "in English, in nontechnical, understandable language, and shall not be promotional in tone or content." Id. § 208.20(a)(1). The manufacturer of a drug for which a medication guide is required must "obtain FDA approval of the Medication Guide before the Medication Guide may be distributed." Id. § 208.24(a). For purposes of this Opinion, the term "label" and "labeling" are used interchangeably.

dosing recommendations and discussed the results of the controversial ARISTOTLE study. The warnings that are pertinent to the present motion to dismiss are described here.[8]

A. Warnings about Bleeding Risks

The Eliquis label warns about the risk of serious bleeding no less than five times. First, in the "Highlights of Prescribing Information" section, under the "Warnings and Precautions" heading, the label states that "ELIQUIS can cause serious, potentially fatal bleeding." In the "Full Prescribing Information" section of the label, there is a heading entitled "Warnings and Precautions" with a subheading entitled "Bleeding." This subheading provides: "ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding." Under the "Adverse Reactions" heading, the label states: "The most serious adverse reactions reported with ELIQUIS were related to bleeding." Also under the "Adverse Reactions" heading, the "Clinical Trials Experience" subheading explains that the "most common reason for treatment

[8] The SAC addresses the December 2012 Eliquis label. The label has since been updated five times: January 2014, August 2014, June 2015, September 2015, and July 2016. See "Eliquis (apixaban) Tablets: Detailed View: Safety Labeling Changes Approved by FDA Center for Drug Evaluation and Research (CDER)," Food & Drug Admin., https://wayback.archive-it.org/7993/20161023083328/http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm384790.htm (last visited May 7, 2017). None of the parties asserts that any of those labeling changes are relevant to the claims in this litigation.

discontinuation in both [clinical] studies was for bleeding-related adverse reactions." Under the "Overdosage" heading, the label states that "[o]verdose of ELIQUIS increases the risk of bleeding." Finally, under the "Patient Counseling Information" heading, the label advises physicians to inform their patients that "it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS." It also instructs physicians to "[a]dvise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician."

B. Warnings about Concomitant Therapy

In addition to warning generally about the risk of bleeding, the Eliquis label also specifically warns about the risk of bleeding when Eliquis is used in conjunction with antiplatelet agents, such as aspirin. The "Bleeding" subheading provides that:

> Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Furthermore, the "Anticoagulants and Antiplatelet Agents" subheading asserts that "[c]oadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding," and that in the

ARISTOTLE study, for example, "concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year."

C. Warnings about the Lack of an Effective Antidote

The Eliquis label twice warns about the fact that there is no specific antidote to Eliquis. First, under the "Bleeding" subheading, the label unambiguously states: "A specific antidote for ELIQUIS is not available," and "[t]here is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose . . . ." Second, under the "Overdosage" heading, the label states: "There is no antidote to ELIQUIS."

In addition to warning about the lack of a specific antidote, the label also discusses potential reversal strategies and to what extent these strategies are supported by clinical research:

> Because of high plasma protein binding, apixaban is not expected to be dialyzable . . . . Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption

> of apixaban, thereby lowering apixaban plasma concentration . . . .

D. Dosing Recommendations

Under the heading "Dosage and Administration," the Eliquis label recommends dosing adjustments for older and higher risk patients. While the recommended dose for most patients is 5 mg taken orally twice daily, a twice daily dose of 2.5 mg is recommended for patients with any two of the following characteristics: (1) 80 years or older; (2) 60 kg or less; (3) serum creatinine levels of 1.5 mg/dL or more. The label further advises that when Eliquis is coadministered with drugs that are strong dual inhibitors of "CYP3A4" and "P-gp," the recommended dose is 2.5 mg twice daily.

E. No Way to Measure or Monitor the Anticoagulation Effect of Eliquis

The "Pharmacodynamics" heading of the label advises that "apixaban prolongs clotting tests such as prothrombin time (PT, INR, and activated partial thromboplastin time (aPTT)," and that "[c]hanges observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban." The label further advises that the Rotachrom Heparin

chromogenic assay "is not recommended for assessing the anticoagulant effect of apixaban."

F. The ARISTOTLE Study

The Eliquis label discusses the ARISTOTLE study at length. Some of the reported findings from the ARISTOTLE trial include that:

> ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism . . . . Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

The label also reports that in the ARISTOTLE trial, Eliquis showed "significantly fewer major bleeds than warfarin."

III. Procedural History

The plaintiffs filed their complaint on July 15, 2016. On October 5, the defendants filed a motion to dismiss the initial complaint pursuant to Rules 12(b)(6) and 9(b). On October 13, the defendants moved the Judicial Panel on Multidistrict Litigation ("JPML") to transfer and coordinate what were then 34 actions pending in 13 different districts -- including the instant action -- pursuant to 28 U.S.C. § 1407. On October 21, the parties in the instant action filed a letter requesting that the Honorable Lewis A. Kaplan stay all proceedings pending

resolution of the JPML petition. The request to enter a stay was denied on October 28.

On November 21, the case was reassigned to this Court as related to sixteen other product liability cases filed in this district concerning the medication Eliquis. That same day, this Court issued an Order instructing the parties in this case and all related actions to confer and identify one or two actions to proceed with early motion practice.[9] The November 21 Order also explained that the initiation of discovery in all actions would turn on whether or not the Court denies the selected motions to dismiss. On December 2, the parties agreed to proceed with a motion to dismiss in the Utts action.

On December 23, the Court issued its Opinion in Utts, granting in part the October 5 motion to dismiss and giving the plaintiffs leave to amend all claims except for the design defect claim, which was entirely preempted. Utts v. Bristol-Myers Squibb Co. & Pfizer Inc., 16cv5668 (DLC), 2016 WL 7429449, at *11-12 (S.D.N.Y. Dec. 23, 2016) ("Utts"). An amended complaint was filed on January 20, 2017.

[9] If the parties could not agree on a single action, the Court permitted the plaintiffs (collectively) and the defendants to each designate an action to proceed immediately with motion practice.

On February 3, the defendants filed a renewed motion to dismiss the amended complaint pursuant to Rules 12(b)(6) and 9(b). On February 6, the Court issued an Order granting the plaintiffs leave to file a second amended complaint by February 24, noting that it would be unlikely that the plaintiffs would have a further opportunity to amend. On February 7, the multidistrict litigation panel issued an order transferring In re: Eliquis Products Liability Litigation, 17md2754, to this Court.

The SAC was filed on February 24. The SAC asserts ten causes of action against the defendants: (1) manufacturing defect; (2) failure to warn; (3) strict liability; (4) negligence and gross negligence; (5) breach of express warranty; (6) breach of implied warranty; (7) fraud/fraudulent concealment; (8) negligent misrepresentation; (9) violation of consumer protection laws; and (10) loss of consortium. In pleading these claims, the plaintiffs rely on nine articles or documents to assert what they contend is a plausible claim that the Eliquis labeling fails to adequately warn of the risk of excessive bleeding. The plaintiffs have since withdrawn their manufacturing defect cause of action. In addition to compensatory damages, the plaintiffs seek punitive damages.

On March 10, the defendants filed a renewed motion to dismiss the SAC. They urge that the plaintiffs' claims are preempted. Analyzing each of the documents on which the plaintiffs have relied to state a claim, the defendants contend that the information in those documents does not constitute newly acquired information and therefore, the federal law of preemption bars the plaintiffs' state law claims. In addition, even if the plaintiffs' claims were not preempted, the defendants argue that they must be dismissed because the warnings given on the Eliquis label were, as a matter of law, sufficient to warn of the risks associated with excessive bleeding on which the plaintiffs' claims are premised. Finally, the defendants argue that the SAC fails to meet the relevant pleading standards. The March 10 motion to dismiss became fully submitted on April 18.

DISCUSSION

The discussion of this motion begins by describing the federal pleading standards and identifying which state's law governs the Utts' claims in the SAC. The Opinion then turns to the issue of preemption. As background to the preemption discussion, the Opinion outlines the FDA's regulatory regime for brand name pharmaceutical drugs. It then applies the law of preemption to the SAC's state law claims, and also analyzes

whether it pleads plausible claims for relief under federal pleading standards.

When deciding a motion to dismiss, a court must "accept all allegations in the complaint as true and draw all inferences in the non-moving party's favor." LaFaro v. N.Y. Cardiothoracic Grp., PLLC, 570 F.3d 471, 475 (2d Cir. 2009) (citation omitted). "To survive a motion to dismiss under Rule 12(b)(6), a complaint must allege sufficient facts which, taken as true, state a plausible claim for relief." Keiler, 751 F.3d at 68. See also Ashcroft v. Iqbal, 556 U.S. 662, 678 (2009) ("[A] complaint must contain sufficient factual matter, accepted as true, to state a claim to relief that is plausible on its face." (citation omitted)). A claim has facial plausibility when "the factual content" of the complaint "allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." Tongue v. Sanofi, 816 F.3d 199, 209 (2d Cir. 2016) (citation omitted).

The plausibility standard is not a "probability requirement"; "[i]t simply calls for enough fact to raise a reasonable expectation that discovery will reveal evidence supporting a plaintiff's claim for relief." Pension Benefit Guar. Corp. ex rel. St. Vincent Catholic Med. Ctrs. Retirement Plan v. Morgan Stanley Inv. Mgmt. Inc., 712 F.3d 705, 729 (2d Cir. 2013) (citation omitted). Nevertheless, "[w]here a

complaint pleads facts that are merely consistent with a defendant's liability, it stops short of the line between possibility and plausibility of entitlement to relief." Iqbal, 556 U.S. at 678 (citation omitted). In sum, "a plaintiff's obligation to provide the grounds of his entitlement to relief requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." Bell Atl. Corp. v. Twombly, 550 U.S. 544, 555 (2007) (citation omitted).

To satisfy the requirements of Rule 9(b), which applies to any pleading of fraud, the complaint must: (1) detail the events giving rise to the fraud, such as the statement/omission that is alleged to be fraudulent, the identity of the speaker, the location of the fraud, and the reason the statement is fraudulent; and (2) allege facts "that give rise to a strong inference of fraudulent intent." Loreley Fin. (Jersey) No. 3 Ltd. v. Wells Fargo Sec., LLC, 797 F.3d 160, 171 (2d Cir. 2015) (citation omitted).

In deciding a motion to dismiss, the court considers "any written instrument attached to the complaint as an exhibit or any statements or documents incorporated in it by reference." Stratte-McClure v. Morgan Stanley, 776 F.3d 94, 100 (2d Cir. 2015) (citation omitted). The court may also consider

"documents upon which the complaint relies and which are integral to the complaint." Subaru Distribs. Corp. v. Subaru of Am., Inc., 425 F.3d 119, 122 (2d Cir. 2005). The Eliquis labeling is integral to the SAC.

I. Choice of Law

Mr. Utts is a resident of California and asserts violations of California consumer protection laws. Moreover, both parties rely on California law in their briefing. Accordingly, there is no dispute that the SAC's claims arise from California statutory and common law.

II. FDA Approval Process

The Food, Drug, and Cosmetic Act of 1938 ("FDCA") is a federal law that regulates the manufacture, use, or sale of drugs. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 196 (2005). To obtain authorization to market a new drug, a drugmaker must submit a new drug application ("NDA"). Such applications must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A). The manufacturer's NDA must demonstrate that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." Id. § 355(d). The manufacturer's NDA must also prove the drug's effectiveness by "substantial evidence that the drug will have

the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." Id.

Drug manufacturers must also submit proposed labeling, with annotations, to be used with the drug. Id. § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i). The FDA's premarket approval of an NDA includes the approval of the exact text in the proposed label. See 21 U.S.C. § 355; 21 C.F.R. § 314.105(b). In making a detailed review of proposed labeling, the FDA seeks to allow "only information for which there is a scientific basis to be included." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008) (hereinafter, "Labeling Changes").

The labeling must include certain categories of information organized into predetermined headings and subheadings. See 21 C.F.R. §§ 201.56, 201.57, and 201.80. For example, the "Warnings and Precautions" section of a label must describe

> clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification).

Id. § 201.57(c)(6)(i).

The "Adverse Reactions" section requires a description of "the overall adverse reaction profile of the drug based on the entire safety database." Id. § 201.57(c)(7). An "adverse reaction" is defined as an "undesirable effect, reasonably associated with use of a drug." Id. "This definition does not include all adverse events observed during use of a drug," but rather "only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." Id. In addition, "any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies . . . ." Id. § 201.57(c)(7)(iii).

After approval, manufacturers are required to maintain records and disclose to the FDA any adverse health consequences reported during the prescription drug's use. 21 U.S.C. § 355(k)(1); 21 C.F.R. §§ 314.80(c), 314.81. If, on the basis of these disclosures, the FDA learns of new safety information which it believes should be included in the labeling of the drug, it retains the authority to require amendments to the drug's label. 21 U.S.C. § 355(o)(4); Wyeth v. Levine, 555 U.S. 555, 567 (2009) (observing that the 2007 FDCA amendments for the first time "granted the FDA statutory authority to require a manufacturer to change its drug label based on safety

information that becomes available after a drug's initial approval."). Alternatively, if the FDA finds that the drug is not "safe" when used in accordance with its labeling, or if, on the basis of new information, the FDA finds that the labeling of such drug is "false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of," the agency "shall" withdraw its approval of the drug. 21 U.S.C. § 355(e). In addition, the FDA "shall" deem a drug "misbranded" if "it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling." Id. § 352(j).

Notwithstanding the FDA's post-approval oversight and regulation, "manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." Wyeth, 555 U.S. at 579; see also 21 U.S.C. § 355(o)(4)(I) (providing a rule of construction clarifying that the 2007 amendments to the FDCA "shall not be construed to affect the responsibility of the responsible person or the holder of the approved application . . . to maintain its label in accordance with existing requirements"). Thus, the manufacturer is charged "both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." Wyeth, 555 U.S. at 571.

There are two ways for a manufacturer to fulfill its post-FDA approval labeling duties. Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application. See 21 C.F.R. § 314.70(b). A manufacturer may, however, make certain changes to its label without prior agency approval through the "changes being effected" ("CBE") regulation. The CBE regulation allows a manufacturer to change its label unilaterally to "add or strengthen a contraindication, warning, precaution, or adverse reaction," id. § 314.70(c)(6)(iii)(A), as soon as there is "reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established," id. § 201.57(c)(6)(i). A manufacturer may also, pursuant to the CBE regulation, "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," id. § 314.70(c)(6)(iii)(C), or "delete false, misleading, or unsupported indications for use or claims for effectiveness," id. § 314.70(c)(6)(iii)(D).

Labeling changes pursuant to the CBE regulation may only be made on the basis of "newly acquired information." Id. § 314.70(c)(6)(iii). "Newly acquired information" is defined as:

> [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 (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.

Id. § 314.3(b). Information previously known to the manufacturer, but not submitted to the FDA, may constitute "newly acquired information," provided that the information meets the other CBE requirements. Labeling Changes, 73 Fed. Reg. at 49606.

The FDA has recognized that "[e]xaggeration 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." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008). Indeed, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance." Id. For this reason, the CBE regulation requires that there be sufficient evidence of a causal association between the drug and the information sought to be added. Id.; see also 21 C.F.R. § 201.57(c)(6)(i). Moreover, the FDA retains the authority to reject labeling changes made pursuant to the CBE regulations. Wyeth, 555

U.S. at 571. By expressly requiring that a CBE supplement only reflect newly acquired information and "be based on sufficient evidence of a causal association," the FDA ensures "that scientifically accurate information appears in the approved labeling." Labeling Changes, 73 Fed. Reg. at 49604.

III. Federal Preemption of Pharmaceutical Claims

The Supremacy Clause 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. "A fundamental principle of the Constitution is that Congress has the power to preempt state law." Crosby v. Nat'l Foreign Trade Council, 530 U.S. 363, 372 (2000). State law is preempted by federal law when Congress intends federal law to "occupy the field," or where state law conflicts with a federal statute. Id. (citation omitted).

Conflict preemption exists "where it is impossible for a private party to comply with both state and federal law and where, under the circumstances of a particular case, the challenged state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." Id. (citation omitted). "Impossibility pre-emption is a demanding defense." Wyeth, 555 U.S. at 573. Courts must "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." Id. at 565 (citation omitted). "[T]he historic police powers of the State include the regulation of matters of health and safety." De Buono v. NYSA-ILA Med. & Clinical Servs. Fund, 520 U.S. 806, 814 (1997). As the Supreme Court has explained,

> [t]hroughout our history the several States have exercised their police powers to protect the health and safety of their citizens. Because these are primarily, and historically, matters of local concern, the States traditionally have had great latitude under their police powers to legislate as to the protection of the lives, limbs, health, comfort, and quiet of all persons.

Medtronic, Inc. v. Lohr, 518 U.S. 470, 475 (1996) (citation omitted).

In a recent trilogy of opinions, the Supreme Court addressed the issue of conflict preemption in the context of state product liability claims against drug manufacturers. As described in more detail in Utts, the Supreme Court's decisions in Wyeth, 555 U.S. 555, PLIVA, Inc. v. Mensing, 564 U.S. 604 (2011), and Mutual Pharmaceutical Co., Inc. v. Bartlett, 133 S. Ct. 2466 (2013), read holistically, indicate that federal law preempts all pre-FDA approval failure to warn and design defect claims for branded prescription medication. See Utts, 2016 WL 7429449, at *6. As Utts explains, brand name drug manufacturers lack the authority to alter a drug's design or a label's

warnings at the time the NDA approval process concludes. Id. at *9; see Labeling Changes, 73 Fed. Reg. at 49606 ("State law claims that challenge labeling that FDA approved after being informed of the relevant risk are preempted." (citation omitted)). Thereafter, however, depending on the significance of the change to the drug's design or the type of change in a label, federal regulations permit -- and indeed, require -- manufacturers to unilaterally alter the design and label. Thus, there may be no preemption of state product liability law where the plaintiffs' claims are based on newly acquired information that, pursuant to the CBE regulation, the defendants could unilaterally make without FDA approval. Utts, 2016 WL 7429449, at *9.

Post-FDA approval preemption analysis proceeds in two stages. First, the plaintiff must show that there existed "newly acquired information" such that the defendants could unilaterally change the label pursuant to the CBE regulation without FDA approval. But, the mere availability of a CBE label amendment does not necessarily defeat a manufacturer's preemption defense. Because the FDA "retains the authority to reject labeling changes," a manufacturer may still -- even after the plaintiff has identified "newly acquired information" -- establish an impossibility preemption defense through "clear evidence that the FDA would not have approved a change" to the

label. Wyeth, 555 U.S. at 571; see also In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig., 852 F.3d 268, 283-84 (3d Cir. 2017). In sum, if the plaintiff can point to the existence of "newly acquired information" to support a labeling change under the CBE regulation, the burden then shifts to the manufacturer to show by "clear evidence" that the FDA would not have approved the labeling change made on the basis of this newly acquired information.

IV. California Product Liability: Failure to Warn

California recognizes three theories of product liability: failure to warn, design defect, and manufacturing defect. The SAC asserts only a failure to warn theory of product liability.[10] Its failure to warn claim is at the heart of the SAC and the principal focus of the parties' briefing on the motion to dismiss.

Failure to warn arises when a manufacturer has issued no warnings or has failed to adequately warn of dangers posed by its product. See Anderson v. Owens-Corning Fiberglas Corp., 53 Cal. 3d 987, 996 (1991). Under California law, a prescription

[10] Although the plaintiffs alleged a manufacturing defect claim in the SAC, they withdrew this cause of action in their memorandum of law in opposition to this motion. The plaintiffs have also abandoned any design defect cause of action in accordance with this Court's ruling in Utts. See Utts, 2016 WL 7429449, at *11-12 (finding all design defect claims preempted and dismissing the plaintiffs' design defect cause of action without leave to amend).

drug manufacturer is strictly liable if it failed to "adequately warn of a particular risk that was known or knowable in light of the generally recognized and prevailing best scientific and medical knowledge available at the time of manufacture and distribution." Carlin v. Superior Court, 13 Cal. 4th 1104, 1112 (1996) (emphasis added). Failure to warn based on a negligence theory "requires a plaintiff to prove that a manufacturer or distributor did not warn of a particular risk for reasons which fell below the acceptable standard of care, i.e., what a reasonably prudent manufacturer would have known and warned about." Anderson, 53 Cal. 3d at 1002.

Under California law, application of the failure to warn theory to pharmaceuticals requires the court to determine:

> whether available evidence established a causal link between an alleged side effect and a prescription drug, whether any warning should have been given, and, if so, whether the warning was adequate. These are issues of fact involving, inter alia, questions concerning the state of the art, i.e., what was known or reasonably knowable by the application of scientific and medical knowledge available at the time of manufacture and distribution of the prescription drug. They also necessarily involve questions concerning whether the risk, in light of accepted scientific norms, was more than merely speculative or conjectural, or so remote and insignificant as to be negligible.

Carlin, 13 Cal. 4th at 1116.

As the California Supreme Court has acknowledged, in the failure-to-warn context, strict liability is, to some extent, "a

hybrid of traditional strict liability and negligence doctrine" since "the knowledge or knowability requirement for failure to warn infuses some negligence concepts into strict liability cases." Id. at 1111-12. The knowledge or knowability requirement holds a drug manufacturer to the standard of "knowledge and skill of an expert in the field," and further obligates the manufacturer "to keep abreast of any scientific discoveries" and to "know the results of all such advances." Id. at 1113 n.3. The manufacturer's knowledge "must exist at the time of distribution." Id. "[S]ubsequently developed scientific data [is not] controlling." Id. In sum, the primary difference between a failure to warn action premised on strict liability and a failure to warn action sounding in negligence is that strict liability "is not concerned with the standard of due care or the reasonableness of a manufacturer's conduct." Id. at 1112.

Even where a risk is "known" or "knowable" at the time of distribution, under California law, a manufacturer "may not be held liable for failing to give a warning it has been expressly precluded by the FDA from giving." Id. at 1115 n.4. Thus, if the manufacturer disclosed to the FDA "state-of-the-art scientific data concerning the alleged risk" and the FDA determined, after its review, "that the pharmaceutical manufacturer was not permitted to warn -- e.g., because the data

was inconclusive or the risk was too speculative to justify a warning," then the manufacturer could not be held strictly liable for failure to warn. Id. at 1115. "[T]he FDA's conclusion that there was, in effect, no 'known risk' is controlling." Id.

California also follows the learned intermediary doctrine, which provides that "in the case of prescription drugs, the duty to warn runs to the physician, not to the patient." Id. at 1116. Therefore, a manufacturer discharges its duty to warn if it provides adequate warnings to the physician about any known or reasonably knowable dangerous side effects, regardless of whether the warning reaches the patient. Finally, "a pharmaceutical manufacturer may not be required to provide warning of a risk known to the medical community." Id.

A. The Plaintiffs' Failure to Warn Claims Are Preempted.

The defendants first assert that the plaintiffs' California failure to warn claims are preempted by federal law because the information on which the SAC relies to plead its claims is not "newly acquired information," as that term is defined under the CBE regulations. The "newly acquired information," which is information that was not submitted to the FDA prior to the FDA's approval of the drug and its label, must reveal risks of a "different type or greater severity or frequency than previously included in submissions to [the] FDA." 21 C.F.R. § 314.3(b).

The SAC identifies 34 warnings that the defendants allegedly failed to provide in the Eliquis label. In opposition to this motion, the plaintiffs largely abandon the failure to warn claims directed toward the risk of excessive bleeding and the lack of an effective reversal agent. They instead focus on three categories of warnings: (1) monitoring; (2) advice regarding bleeding reversal strategies; and (3) dosage recommendations.

The SAC relies exclusively on nine reports, studies, and articles as the bases for its assertion that the Eliquis labeling was inadequate in failing to give these warnings. Most of these documents are appended as exhibits to the SAC. The information contained in this literature does not constitute "newly acquired information" under the FDA's CBE regulation. Accordingly, the plaintiffs' claims are preempted because federal law would not have permitted the defendants to make any change to the Eliquis label.

The SAC and the plaintiffs in their brief in opposition to this motion give the greatest emphasis to a single report, and it is to that report that this Opinion turns first. The remainder of the nine documents or reports are given relatively limited weight in the SAC and in the plaintiffs' brief, and will be addressed thereafter. For five of these reports, the plaintiffs do not actually contend either in the SAC or in

opposition to this motion that they contain newly acquired information. Those five are discussed last.

1. Allegation of Newly Acquired Information

a. The Institute for Safe Medical Practices QuarterWatch Report (the "ISMP Report")

The plaintiffs rely heavily on four statements in the ISMP Report to support their claim that the defendants have not fully disclosed the incidence of bleeding in users of Eliquis. The ISMP Report, published in September 2015, analyzed "adverse drug event" data for NOACs from the third and fourth quarters of 2014. Before assessing whether the four statements constitute newly acquired information, the function of ISMP reports will be described.

ISMP reports draw upon "adverse drug event" reports, among other sources of information, to describe drug safety issues. Federal regulations require drug manufacturers to report "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related" to the FDA. 21 C.F.R. § 314.80(a), (c). All reported adverse drug events are uploaded to the FDA Adverse Event Reporting System ("FAERS") database. See "Questions and Answers on FDA's Adverse Event Reporting System (FAERS)," U.S. Food & Drug Admin., https://www.fda.gov/drugs/guidancecompliance-

regulatoryinformation/surveillance/adversedrugeffects (last visited May 7, 2017) (hereinafter, "FDA Website").

Federal regulations advise that a report submitted by a manufacturer "does not necessarily reflect a conclusion by the [manufacturer] or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect." 21 C.F.R. § 314.80(l). As the FDA Website explains:

> FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event.

The Supreme Court has similarly warned that "[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." Matrixx Initiatives, Inc. v. Siracusano, 563 U.S. 27, 44 (2011). In sum, "the mere existence of reports of adverse events . . . says nothing in and of itself about whether the drug is causing the adverse events." Id.

The ISMP Report acknowledges the limitations of its analysis of adverse event report data: "The submission of an individual report does not in itself establish that the suspect drug caused the event described." The ISMP Report

therefore recommends that its findings "be interpreted in light of the known limitations of a reporting system that does not collect data systemically." The ISMP Report further acknowledges that "[w]hile the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population."

Among the categories of pharmaceuticals it discussed, the ISMP Report compared adverse event reports across three NOACs -- Xarelto, Pradaxa, and Eliquis. It found that Eliquis "showed the strongest safety profile from several perspectives" and "had the best adverse event safety profile by several measures." Not only did Eliquis have the fewest reports in the FAERS database -- even after adjusting for prescription volume -- but it also had the fewest direct reports[11] to the FDA, the fewest deaths, and the lowest percentage of deaths.

[11] Healthcare professionals and consumers may voluntarily report adverse drug experiences to the FDA. If a healthcare professional or consumer instead chooses to report an adverse drug experience to the manufacturer, the manufacturer must report the data to the FDA. According to the ISMP Report, direct reports to the FDA from health professionals and consumers are "of higher quality" and "provide signals of safety issues that are independent of manufacturer marketing and other patient contact programs that can skew results."

i. Comparison of Eliquis and Xarelto

The ISMP Report first relies upon a table comparing NOAC pharmaceutical adverse event reports to argue that the defendants failed to adequately warn about the bleeding risks associated with Eliquis. The table lists adverse event reports for Xarelto (rivaroxaban), Pradaxa (dabigatran), and Eliquis (apixaban) across several events, such as death outcomes, embolic-thrombotic events, and hemorrhaging events.[12] The ISMP Report observed that, when the adverse event reports were examined, the difference between Xarelto and Eliquis "in percentage of deaths and total hemorrhage cases were small." It observed as well, however, that Eliquis had the "best adverse event safety profile by several measures," even when adjusted for prescription volume.

In the SAC, the plaintiffs allege that the fact that Eliquis and Xarelto have a comparable incidence of death outcomes and hemorrhaging in their adverse event reports is "critical because real-world signal data from Xarelto was

[12] For example, the table provides that, when examining the adverse event reports, there were 379 death outcomes for Xarelto users (approximately 11.4%) compared to 108 death outcomes for Eliquis users (approximately 10.7%). The table further provides that there were 1,647 hemorrhage events (approximately 49.4%) for Xarelto users, and 492 hemorrhage events (approximately 48.5%) for Eliquis users.

also found to have a much high[er] incidence of adverse events than reported in the clinical studies."[13] Xarelto's real world performance as compared to the clinical studies of Xarelto says nothing about how the real world performance of Eliquis compares to the clinical data disclosed by the defendants to the FDA. The table and the description from the ISMP report do not suggest -- nor do the plaintiffs allege -- that the real-world signal data for Eliquis shows a greater severity or frequency of bleeding events or deaths than previously disclosed in Eliquis' submissions to the FDA. 21 C.F.R. § 314.3(b). Accordingly, the information contained in this table does not constitute newly acquired information.

ii. Concomitant Use of Eliquis and Antiplatelet Agents

According to the SAC, the ISMP Report "found that Eliquis, when used in conjunction with commonly used platelet inhibitors [aspirin, NSAIDs, and SSRIs, among others]," shows a "significantly increased risk of bleeding events compared to" the clinical data from the ARISTOTLE

[13] For this assertion, the SAC relies on a 2013 news report, citing data "from a federal authority," that Xarelto's manufacturer faced a growing number of reports of "suspected undesirable side-effects."

study. (Brackets in original.) This assertion is a misreading of the ISMP Report and the Eliquis label.

In evaluating the adverse event data, the ISMP Report found that "concomitant therapy with platelet inhibitors increased the odds of a hemorrhage event by threefold" in all three NOACs and in warfarin. This "threefold" risk estimate is not specific to Eliquis, but rather is based on combined adverse event data from a number of anticoagulant medications, including warfarin.

Moreover, the Eliquis label specifically warns about the concomitant use of platelet inhibitors and Eliquis:

> Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and nonsteroidal anti-inflammatory drugs (NSAIDs).

(Emphasis added.) Section 7.3 of the Eliquis label -- entitled "Anticoagulants and Antiplatelet Agents" -- further states that "[c]oadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding."

In connection with its discussion of concomitant therapy, the Eliquis label also cites the results from two clinical studies: ARISTOTLE and APPRAISE-2. While the ARISTOTLE study found less than a twofold increase, the

APPRAISE-2 trial found over a fourfold increase in major bleeding, which is greater than the "threefold" ratio cited in the ISMP Report. Thus, even if one were to assume that the "threefold" estimate cited in the ISMP Report accurately represents the Eliquis-specific bleeding rate, this would still not constitute "newly acquired information," as the Eliquis label already discloses a higher risk of bleeding than that contained in the ISMP Report. See 21 C.F.R. § 314.3(b) (providing that newly acquired information must reveal risk of a "greater severity or frequency than previously included in submissions to FDA").

In opposition to this motion, the plaintiffs appear to abandon their assertion that the ISMP Report contains new information regarding the increased risk of bleeding when Eliquis is used in combination with antiplatelet agents. They instead argue that the guidance regarding concomitant use of antiplatelet agents is inadequate because the label "does not advise how or when to use combination therapy with Eliquis" or "how commonly bleeding events will occur."[14] This omission in

[14] The plaintiffs point to the following sentence from the ISMP Report in support of their argument that the Eliquis labeling inadequately warns about the risks of concomitant therapy:

> The prescribing information for all three [NOACs] contains no guidance on the concomitant use of

guidance was evident to the FDA when it approved the label and the plaintiffs have not identified any newly acquired information from the ISMP Report that would support a label change.[15]

iii. Improved Dosage Guidance

The SAC next relies on the ISMP Report to complain that the Eliquis label does not "mention . . . potential problems because of Eliquis' one size fits all dosing." As described above, however, Eliquis has two recommended dosing regimens -- not just one. In any event, this section of the Report provides no newly acquired information that would support a label change regarding dosing.

In its discussion of NOAC dosing regimens, the ISMP Report found that apixaban avoided some of the pharmacological issues that the earlier NOACs had confronted. For example, rivaroxaban and dabigatran were found to have "problems in basic pharmacology that raised questions about their suitability for simple dosing regimens without adjusting for each patient." By contrast, apixaban "appeared to avoid the limitations observed

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antiplatelet agents other than a warning that an increased risk of bleeding was observed.

[15] Although proffered as a failure to warn claim, this and several other contentions in the SAC are essentially criticisms of the design of apixaban. Design claims are preempted. Utts, 2016 WL 7429449, at *11-12.

for rivaroxaban and dabigatran," in part because apixaban was tested in both once- and twice-daily regimens. This section of the Report concludes with the following observation: "[U]nanswered is whether apixaban safety could be further improved with individualizing the dose for each patient, as is done with warfarin." This observation does not constitute newly acquired information, as it simply speculates whether apixaban safety could be further improved.

iv. Comparison with Warfarin

Finally, the SAC relies on the ISMP Report to contend that the Eliquis label does not "accurately reflect" that treatment with Eliquis increases the risk of a bleeding event for a patient when compared to "the venerable warfarin blood thinner." The statement cited from the Report does not, however, concern a bleeding event, and in any event does not reflect any newly acquired information.

The ISMP Report compared adverse event reports for the three NOACs against warfarin. One of the NOACs (not Eliquis) had a significantly worse outcome compared to warfarin when reports regarding embolic-thrombotic events were examined. Eliquis and another NOAC had "increased odds of embolic-thrombotic events compared to warfarin, but less so." As the defendants point out in their motion, and the plaintiffs do not

dispute, embolic-thrombotic events are ischemic strokes[16] and not bleeding events. Nor do the plaintiffs argue that any of this data comparing the incidence of embolic-thrombotic events for Eliquis and warfarin constitutes newly acquired information. In sum, data on ischemic strokes could not form the basis for a CBE label change related to bleeding risks.

b. British Medical Journal Study (the "BMJ Study")

The second study on which the SAC relies is the BMJ Study, which was published in 2016. According to the SAC, the BMJ Study's finding that NOACs were "not significantly different from warfarin" in terms of the risk of ischemic stroke in patients with atrial fibrillation contradicts Eliquis' "promotional materials."[17] The plaintiffs do not assert that there is any deficiency in this regard in the Eliquis labeling. Nor, as explained here, could they.

[16] There are two types of strokes: ischemic strokes and hemorrhagic strokes. Ischemic strokes are caused by blockage of an artery, whereas hemorrhagic strokes are caused by bleeding. There are two types of ischemic strokes: thrombotic and embolic. In a thrombotic stroke, a blood clot forms inside one of the brain's arteries. Embolic strokes are caused by a blockage that forms elsewhere in the body and travels through the bloodstream to the brain.

[17] The plaintiffs' claims regarding the defendants' promotional materials are addressed below in connection with the SAC's claims of fraud and violation of California's consumer protection laws.

The BMJ Study is an observational study comparing the effectiveness of warfarin and NOACs in patients with non-valvular atrial fibrillation who were "naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism." The BMJ Study found that, for ischemic stroke only, "no significant differences were evident . . . between NOACs and warfarin." Otherwise, "[t]he risks for death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran, compared with warfarin." The BMJ Study concluded that "[a]ll NOACs are generally safe and effective alternatives to warfarin in a clinical care setting."

The finding regarding the risk of ischemic stroke from the BMJ Study is consistent with the data reported in the Eliquis labeling. The Eliquis labeling provides in relevant part:

> Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

(Emphasis added.) Accordingly, the findings directed towards the risk of ischemic stroke for Eliquis users do not constitute newly acquired information.[18]

c. Thrombosis Journal Article

In support of two related arguments, the SAC cites a 2013 article from the Thrombosis Journal entitled "Practical Management of Patients on Apixaban: A Consensus Guide." First, the SAC alleges that the Eliquis label has failed to provide guidance on managing "potentially life threatening bleeding" even though physicians are forming a consensus about "potentially effective avenues" to stop serious injury and death from excessive bleeding. The SAC does not identify the particular "avenues" that it contends should be described in the label. Second, the SAC alleges that, even though the Eliquis label discusses the half-life of apixaban, "certain studies" indicate that it "is currently unknown what level of Eliquis would be considered safe for an elective surgery." An examination of this practical guide for physicians provides no basis to assert

[18] In opposition to this motion, the plaintiffs argue that it is "disingenuous" to focus exclusively on ischemic stroke instead of all strokes. But, the SAC's allegation regarding the BMJ Study concerns only ischemic strokes, and the BMJ Study praises the comparative effectiveness of Eliquis in all other regards.

that there is information about Eliquis that should have been included in the label but was not.

As the guide explains, in the "absence of robust clinical data for emergency and peri-operative management of patients receiving apixaban," an expert panel of Australian clinicians from various fields convened to develop tips on managing bleeding and invasive procedures in patients taking apixaban. The consensus guide notes generally that in clinical trials, apixaban demonstrated a "superior reduction in stroke and systemic embolism, compared to warfarin," and that apixaban resulted in "significantly less major bleeding, compared to warfarin."

The consensus guide contains a flowchart entitled "Considerations for the Management of Bleeding, Based on Expert Consensus." The article observes as well that "[a] specific antidote for apixaban is not currently available" and that "[i]n the absence of published data regarding the treatment of patients with active bleeding while receiving apixaban, discontinue apixaban, apply standard supportive treatment and other local measures." (Emphasis added.) The plaintiffs do not allege, however, that this expert guidance contains, or is founded upon, any newly acquired information regarding reversal agents or the treatment of excessive bleeding that should be included in a drug label.

Nor is there any basis to allege, based on this guide, that the Eliquis label's statements regarding either the drug's half-life or its safety in connection with elective surgery are misleading. The Eliquis label contains the following warnings about discontinuation of Eliquis for surgery:

> ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled.

The guide agrees that the label correctly describes the half-life for Eliquis, and nothing in it suggests that the label's statement regarding elective surgery is inaccurate in any respect. The guide notes that apixaban "can be ceased for a shorter period of time than warfarin before invasive procedures," but that a "'safe' residual drug level of apixaban for surgery is presently unknown, and no test has been correlated with bleeding risk." It agrees with the label that "[i]n general, apixaban should be discontinued 2 to 3 days prior to elective surgery." The plaintiffs do not allege that this statement contains newly acquired information about what constitutes a safe residual drug level of apixaban in advance of surgery.

d. FDA News Article

In support of its argument that the Eliquis label does not adequately warn about the lack of an effective antidote, the SAC cites to an August 2016 news article about the FDA's failure to approve "an antidote for Eliquis bleeding." This article does not refer to any new information that would have permitted the defendants to amend the Eliquis label. And, in their opposition to this motion, the plaintiffs do not argue that it does. As described above, the label discloses in unambiguous terms that no known antidote for apixaban exists.

e. Pradaxa

Construing the SAC favorably, it may assert that the FDA's approval of an antidote to Pradaxa -- a competing NOAC -- constitutes newly acquired information that should have been included in the Eliquis label.[19] Specifically, the SAC asserts that the Eliquis labeling should mention "this safer alternative NOAC." Insofar as these allegations are directed toward a claim that Eliquis could or should have been designed more safely -- that is, not

[19] Unlike every other failure to warn claim, the SAC does not cite to any articles or reports in support of this claim.

manufactured or distributed without an effective antidote -- such thinly veiled design defect claims are preempted.

But even if analyzed as a failure to warn claim, this information does not constitute "newly acquired information." As described above, the label clearly warns that there is no reversal agent for apixaban. Moreover, federal regulations do not require a manufacturer to include information about a competitor's product or progress. See 21 C.F.R. §§ 201.56, 201.57, and 201.80.

2. No Allegation of Newly Acquired Information

The plaintiffs do not contend that any of the five remaining documents to which the SAC refers contains newly acquired information regarding an undisclosed risk of bleeding. Several of these articles merely express a desire for further investigation into NOAC dosing regimens or reversal agents. As a consequence, none of the reports, studies, or publications upon which the SAC relies help the plaintiffs' failure to warn claims overcome the defendants' preemption motion. Each of the additional pieces of literature is described below.

a. Journal of American Medical Association Internal Medicine Article (the "JAMA Article")

The SAC cites a February 2015 JAMA Article solely for its critique of the ARISTOTLE study. In opposing this

motion, the plaintiffs explain that they are relying on this article to illustrate how some manufacturers may conceal information about clinical studies from the FDA. But, as an examination of the JAMA Article makes clear, its primary critique is with the lack of attention research misconduct receives in the scientific literature. It does not suggest that the FDA was unaware of problems with the ARISTOTLE study when it approved the Eliquis label.

The JAMA Article evaluates whether, and to what extent, peer-reviewed literature reflects FDA findings of research misconduct in clinical trials. The JAMA Article identified several published clinical trials -- including Eliquis' ARISTOTLE trial -- in which an FDA inspection uncovered objectionable conditions or practices at a clinical trial site. With respect to the ARISTOTLE trial, the JAMA Article noted that a clinical site in China "had apparently altered patient records," and that "[i]f one were to exclude the data from the patients at that site, the claim of a statistically significant mortality benefit disappears." Notwithstanding this "fraudulent data," the JAMA Article found that "when [data from] all the suspect Chinese sites are excluded rather than just the one at which the evidence of alleged research misconduct was found, the mortality benefit [of Eliquis] becomes

statistically significant." The JAMA Article criticized the peer-reviewed literature for consistently relying on the full data set from the ARISTOTLE trial without excluding data from the site where the research misconduct was uncovered.

b. FDA Signal Report

The SAC makes a brief reference to a report of an ongoing FDA investigation into the adverse event signal between Eliquis and a health condition known as vasculitis.[20] This does not concern an increased or undisclosed risk of bleeding, and the plaintiffs do not contend that it does.

In November 2016, the FDA announced that it had identified a potential signal of a "serious risk/new safety information" for vasculitis in patients taking Eliquis, Pradaxa, Savaysa, and Xarelto based on adverse event reports from July to September 2016. See https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm534355.htm (last visited May 7, 2017). The FDA reported that it is "evaluating the need for regulatory action." This announcement, which if anything confirms that the FDA is engaged in ongoing

[20] Vasculitis is a condition that involves inflammation in the blood vessels. Inflammation can cause the vessel to narrow or close off, thereby restricting or preventing blood flow through the vessel.

monitoring of Eliquis and other NOACs, does not constitute evidence that could support a labeling change regarding bleeding risks in Eliquis users. As the plaintiffs have clarified in their opposition to this motion, they rely on the 2016 FDA Signal Report "to indicate that FDA oversight of Eliquis is ongoing."

c. Annals of Hematology Article

The SAC points to a scientific journal article to support its proposition that it "would be beneficial" for NOACs, including Eliquis, to have a "more tailored" dosing regimen.[21] The article, published in 2015 in the Annals of Hematology, is entitled: "How to Choose Appropriate Direct Oral Anticoagulant for Patient with Nonvalvular Atrial Fibrillation." It offers guidance on the most appropriate NOAC for individual non-valvular atrial fibrillation patients based on clinical trial results. In its brief discussion of dosing, the article states that "dose adjustment of rivaroxaban and edoxaban was much better explored than apixaban," and that "this information should be discussed with the patient while deliberating on the

[21] In opposition to this motion, the plaintiffs contend that this article provides a basis to allege that the defendants are in possession of adverse information relating to the "therapeutic dose ranges of Eliquis that is unknown to the FDA" and that they should update their label accordingly. That is not the allegation in the SAC and nothing in the article provides support for this characterization of the article.

choice of a [N]OAC for someone who would require dose modification."

The article does not purport to offer "new analyses of previously submitted data." 21 C.F.R. § 314.3(b). Rather, it explores the limitations of the clinical data and offers guidance to prescribing physicians in light of these limitations. Accordingly, it does not constitute newly acquired information.

d. The BMJ Rivaroxaban Article

Relying on an article published in The BMJ about another NOAC -- rivaroxaban -- the SAC argues that a new dosing regimen for Eliquis that involves regular monitoring and individualized dosage adjustments would "maximize benefit and minimize harm to the patient" and would "seem[] to be a much safer" approach than that currently provided for in the Eliquis label. This argument does not constitute newly acquired information.

The article upon which the SAC relies to make this argument was published in February 2016 and is entitled "Rivaroxaban: Can We Trust the Evidence?" A 2015 investigation uncovered the use of faulty INR[22] measuring

[22] The faulty INR device used in the ROCKET-AF trial was said to deliver results that were "clinically significantly lower" than a laboratory method. An unreliable low reading could mean that patients in the ROCKET-AF trial had their warfarin dose

devices in rivaroxaban's ROCKET-AF trial, which may have caused researchers to overstate the safety of rivaroxaban in comparison to warfarin. As the article points out, however, the ARISTOTLE trial for apixaban did not utilize the faulty device from the ROCKET-AF trial.

The article also briefly alludes to problems with a dabigatran trial in which manufacturers withheld analyses from regulators that suggested that monitoring of anticoagulant activity and dosage adjustment could help prevent major bleeds. The FDA gave its approval to both rivaroxaban and dabigatran before it gave its approval to apixaban.

The article explores the benefits of pursuing tailored dosing in light of the rivaroxaban and dabigatran clinical trial "errors." It describes a 2015 presentation from Robert Temple, deputy director for clinical science at the FDA's Center for Drug Evaluation and Research, which "suggests that the FDA believes there is a scientific argument for measuring the blood levels of these drugs [i.e., NOACs] and adjusting the dose." The article quotes

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increased unnecessarily, thereby increasing the risk of bleeding.

Temple as stating that "early optimization [of dosing] seems worthwhile," and that

> [a]fter a drug is approved, it usually takes a safety signal to prompt significant action on the part of the FDA. It is this lack of safety signal that appears to be hindering the FDA in their desire to pursue tailored dosing for [N]OACs. If it turns out that the issue with the INR device changes the safety profile of rivaroxaban, this may constitute the safety signal necessary for the FDA to act in this regard.

This article does not cite to any Eliquis-specific data. Moreover, as Mr. Temple's remarks suggest, the FDA monitors adverse event data and it is the lack of such data that "appears to be hindering the FDA in their desire to pursue tailored dosing" for NOACs. In sum, an article about rivaroxaban that does not contain any new analyses of Eliquis clinical data or adverse event report data does not constitute newly acquired information.

The plaintiffs' opposition to this motion reveals that they are principally relying on this article for another purpose. They speculate that the defendants may be withholding information from the FDA that is relevant to dosage determinations. The article provides no basis for such an inference, which in any event, has not been alleged in the SAC.

e. Journal of Thrombosis & Thrombolysis Article

Finally, the SAC relies on an article published in the Journal of Thrombosis and Thrombolysis, which offers guidance on anticoagulant reversal strategies, to support its assertion that there is a "growing concern amongst physicians regarding the absence of guidance for dealing with the unstoppable bleeds of Eliquis." Nothing in the article suggests that newly acquired information exists to support a labeling change regarding reversal agents, and the plaintiffs do not contend otherwise. In essence, therefore, the SAC's complaint about a lack of a reversal agent amounts to a preempted design claim.

Published in 2014, the article -- entitled "Novel Oral Anticoagulants: Pharmacology, Coagulation Measures, and Considerations for Reversal" -- provides an overview of "emerging data on reversal strategies that not only influence laboratory coagulation measures, but potentially the clinical manifestations of bleeding as well." In this lengthy article, there is a two-paragraph discussion of Eliquis and reversal strategies. It observes, for example, that "[t]o date, there are no published data supporting common coagulation measures as surrogate markers for bleeding risk."

That currently available data does not provide guidance about anticoagulant reversal strategies does not suggest that this information -- or lack thereof -- was unknown to the FDA when it approved Eliquis for distribution. Indeed, as described above, the Eliquis label warns in detail about the lack of data on reversal strategies. Among other things, it advises that:

> There is no established way to reverse the anticoagulant effect of apixaban . . . . A specific antidote for Eliquis is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable. . . .

B. Preemption May be Decided on a Motion to Dismiss.

The plaintiffs repeatedly argue that the issue of preemption cannot be decided on a motion to dismiss since the preemption inquiry is "necessarily fact-specific" and should therefore be decided no earlier than at summary judgment. They point to the Third Circuit's decision in In re: Fosamax, 852 F.3d 268, as support for their argument that preemption is not a question of law that can be decided by a court.

It is well-established that preemption may be analyzed and decided at the motion to dismiss stage. After all, a "determination regarding preemption is a conclusion of law." Drake v. Lab. Corp. of Am. Holdings, 458 F.3d 48, 56 (2d Cir. 2006); see also Mensing, 564 U.S. 604 (reversing the Fifth Circuit's holding that state tort claims against generic

manufacturers are not preempted -- an issue that had been decided by the district court on a motion to dismiss, see Demahy v. Wyeth Inc., 586 F. Supp. 2d 642 (E.D. La. 2008)). As the Court of Appeals for the Second Circuit has instructed, however, when considering a preemption argument in the context of a motion to dismiss, "the factual allegations relevant to preemption must be viewed in the light most favorable to the plaintiff. A district court may find a claim preempted only if the facts alleged in the complaint do not plausibly give rise to a claim that is not preempted." Galper v. JP Morgan Chase Bank, N.A., 802 F.3d 437, 444 (2d Cir. 2015).

Moreover, contrary to the plaintiffs' assertion in opposition to this motion, In re: Fosamax does not stand for the proposition that preemption cannot be decided on a motion to dismiss. As explained previously, there are two stages to the preemption inquiry. First, a plaintiff must show that newly acquired information exists such that the manufacturer could unilaterally change its label in accordance with the CBE regulation. Wyeth, 555 U.S. at 569-71. If the plaintiff can prove the existence of newly acquired information, the manufacturer may still establish an impossibility preemption defense by presenting "clear evidence" that the FDA would have exercised its authority to reject the labeling change. Id. at 571. It is the second stage of the preemption analysis to which

the Third Circuit's opinion is addressed. In re: Fosamax holds that the Supreme Court's use of the phrase "clear evidence" in Wyeth was intended as a standard of proof that a defendant must meet in order to establish an impossibility preemption defense. As the Third Circuit explains, "[t]he term 'clear evidence' does not refer directly to the type of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate." In re: Fosamax, 852 F.3d at 285. Rather, it "specifies how difficult it will be for the manufacturer to convince the factfinder that the FDA would have rejected a proposed label change." Id. Thus, the "manufacturer must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by 'clear evidence.'" Id.

There was no dispute in In re: Fosamax that both the manufacturer and the FDA were in possession of newly acquired information:

> Both [the manufacturer] and the FDA have long been aware that antiresorptive drugs like Fosamax could theoretically increase the risk of atypical femoral fractures. . . . Between 1995 and 2010, scores of case studies, reports, and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures.

Id. at 274-75. The issue became, therefore, whether there was clear and convincing evidence that the FDA would have rejected the proposed amendment. Id. at 290-91.

In sum, the plaintiffs' failure to warn claims are preempted because the information upon which the SAC 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. While the plaintiffs repeatedly request in opposition to this motion an opportunity to pursue discovery, they are not entitled to discovery on preempted claims. The motion to dismiss mechanism exists to prevent plaintiffs from conducting fishing expeditions to see if they can cobble together meritorious claims. Discovery is burdensome and expensive, and the Federal Rules of Civil Procedure do not provide for it unless the pleading can survive a Rule 12(b)(6) motion. Rule 12(b) is designed specifically to "streamline[] litigation by dispensing with needless discovery and factfinding." Neitzke v. Williams, 490 U.S. 319, 326-27 (1989). As the Supreme Court has observed:

> It is no answer to say that a claim just shy of a plausible entitlement to relief can, if groundless, be weeded out early in the discovery process through careful case management, given the common lament that the success of judicial supervision in checking discovery abuse has been on the modest side. . . . And it is self-evident that the problem of discovery abuse cannot be solved by careful scrutiny of evidence at the summary judgment stage, much less lucid instructions to juries; the threat of discovery expense will push cost-conscious defendants to settle even anemic cases before reaching those proceedings.

Twombly, 550 U.S. at 559 (citation omitted).

C. The Eliquis Label is Adequate as a Matter of Law.

Not only are the plaintiffs' failure to warn claims preempted, they must also be dismissed because the warnings given on the Eliquis label were, as a matter of law, sufficient to warn of the excessive bleeding risks which are the focus of each of the claims brought in the SAC. Under California law, "[a]n adequate warning is a sufficient defense to a strict liability action." Temple v. Velcro USA, Inc., 196 Cal. Rptr. 531, 533 (Ct. App. 1983). If a warning is adequate, it is a "proper disclaimer to any express or implied warranties" and "negate[s] any negligence or willful misconduct." Id. Interpretation of the adequacy of a label, "where extrinsic evidence is unnecessary, is a question of law for the trial court to determine." Id. A written warning is adequate if it directly warns in plain and explicit terms of the specific risk that has caused injury to the plaintiff. Kearl v. Lederle Labs., 218 Cal. Rptr. 453, 467 (Ct. App. 1985). Where, however, a "warning on a drug label is ambiguous . . . the adequacy of the warning becomes a question of fact for the jury." Miles Labs., Inc. v. Superior Court, 184 Cal. Rptr. 98, 104 (Ct. App. 1982).

While the SAC recites a litany of reasons why the Eliquis label is inadequate, almost all of them are iterations of dangers associated with excessive bleeding while taking Eliquis.

As the plaintiffs acknowledge in opposition to this motion, however, the Eliquis label clearly discloses that there is a risk of excessive bleeding and that there is no known antidote if that occurs. The label says without any ambiguity that apixaban "can cause serious, potentially fatal bleeding." In opposition to this motion, therefore, the plaintiffs rely on just three failures to warn.

In asserting that they have adequately pleaded a failure to warn claim, the plaintiffs argue both that the label should have advised physicians to monitor patients on Eliquis and that it should have given more information to physicians about how to treat patients experiencing bleeding. They also speculate that the defendants may be in possession of information suggesting that there is a "safer dosing method," and if so, that such an improved regimen should also have been included in the label.

Before analyzing these three assertions, it is useful to note that the analysis of the adequacy of the Eliquis label under California law substantially overlaps with the just-concluded preemption analysis. In search of a plausible basis for their failure to warn claims, the plaintiffs relied on the nine articles discussed above. The defendants' motion to dismiss examines the articles in detail and argues that the SAC has taken passages out of context and misconstrued the observations in the articles. As already noted, these articles

do not contain newly acquired information to allow the plaintiffs to escape the defendants' preemption motion. Similarly, the defendants are correct in concluding that, to the extent these nine articles describe risks or other pertinent information related to excessive bleeding, those risks and that information are prominently and unambiguously described in the Eliquis label. Thus, the SAC does not plead any plausible basis for a claim that the risks pertaining to excessive bleeding are not included on the Eliquis label and should be added to it. In response, the plaintiffs have opposed this motion by winnowing their failure to warn claims to the three issues to which this Opinion now turns.

1. Monitoring

The plaintiffs contend that the label should have advised physicians to monitor patients closely for the risks associated with excessive bleeding.[23] They reason that in the absence of better information about the frequency of excessive bleeding

[23] In the SAC, the plaintiffs contend that the Eliquis label should have included a boxed and bolded warning "about serious bleeding events associated with Eliquis." The plaintiffs clarify in opposition to this motion that the Eliquis label is inadequate because, unlike the Xarelto and Pradaxa labels, the Eliquis label does not contain a black box warning advising physicians to monitor their patients closely for signs of neurological impairment. The inclusion of a boxed warning requires a supplemental submission to the FDA and FDA approval. See 21 C.F.R. § 314.70(b)(2)(v)(C); id. § 201.57(a)(4).

events, and in the absence of an antidote for Eliquis, it is important to advise physicians to monitor patients.

This fails to state a claim under California law. The label provides, in unambiguous terms, all of the scientifically reliable information that physicians may need to determine how to monitor their patients. The SAC does not plausibly allege otherwise. The risk of excessive bleeding is fully disclosed, as is the absence of an antidote. The half-life of the drug is described, and advice is given about how long before elective surgery use of Eliquis should be discontinued. The label warns that standard blood tests are not useful in monitoring the anticoagulant effect of apixaban and the literature on which the SAC relies does not suggest otherwise.[24] The SAC does not point to any passage in any of the nine articles suggesting that physicians require or should have more information to assist

[24] As the Eliquis label explains, "[a]s a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban." The label further provides that the Rotachrom Heparin chromogenic assay "is not recommended for assessing the anticoagulant effect of apixaban." Moreover, as the Journal of Thrombosis & Thrombolysis article upon which the SAC relies notes, "there are no published data supporting common coagulation measures as surrogate markers for bleeding risk."

them in making monitoring decisions, or otherwise plead a plausible claim regarding monitoring.

2. Lack of Advice Regarding Bleeding Reversal Strategies

The plaintiffs contend that the label is inadequate for failing to advise physicians on how to treat a bleeding event. This Opinion has already analyzed every report cited in the SAC and found no information to suggest that there is an ambiguity or deficiency in the label's warnings about treatment of severe bleeding. The SAC pointed to no information from any of those articles regarding treatment of severe bleeds that should be added to the label to remove an ambiguity or to warn of an undisclosed risk. The only article that addresses the management of bleeding in any detail is the consensus guide published in the Thrombosis Journal. Its recommendation is to discontinue apixaban and apply "standard supportive treatment and other local measures." This does not supply a basis for a plausible claim that the label needed to add further guidance. Tellingly, the SAC does not identify what treatment information should be added to the label.

3. Dosage Recommendations

Finally, in opposition to this motion the plaintiffs speculate that the defendants may have in their possession "adverse information relating to the therapeutic dose ranges of

Eliquis that is unknown to the FDA." If they do possess such information, the plaintiffs reason, the defendants have a duty to warn and update their labels.

As discussed above, the label outlines different dosing regimens for individuals of certain ages, weights, and serum creatinine levels. None of the nine articles or sources of information on which the SAC relies suggests that there is a basis to believe that another, safer dosage regimen is known and should be disclosed. The SAC does not identify any research or data that undermines or contradicts the dosing guidance provided in the label. Accordingly, the plaintiffs cannot plausibly allege that the defendants should have adjusted the dosing recommendations in the Eliquis label. Needless to say, mere speculation about information that the defendants may possess is insufficient to plausibly plead a claim. See Twombly, 550 U.S. at 555 ("Factual allegations must be enough to raise a right to relief above the speculative level . . . .").

V. Breach of Express and Implied Warranties

In order to plead a cause of action for breach of express warranty under California law, the plaintiff must allege: (1) the exact terms of the warranty; (2) the plaintiff's reasonable reliance thereon; and (3) a breach of that warranty which proximately caused plaintiff's injury. Williams v. Beechnut Nutrition Corp., 229 Cal.

Rptr. 605, 608 (Ct. App. 1986). The express warranty must constitute "an affirmation of fact or promise or a description of the goods." Weinstat v. Dentsply Int'l, Inc., 103 Cal. Rptr. 3d 614, 626 (Ct. App. 2010) (citation omitted).

To maintain a claim for breach of implied warranty, a plaintiff must allege (1) that he intended to use the product for a particular purpose; (2) that the defendant had reason to know of this purpose; (3) that the plaintiff relied on defendant's skill or judgment to provide a product suitable for this purpose; (4) that the defendant had reason to know that buyers relied on its skill or judgment; (5) that the product was unfit for the purpose for which it was purchased; and (6) that it subsequently damaged the plaintiff. Keith v. Buchanan, 220 Cal. Rptr. 392, 399 (Ct. App. 1985).

California follows the learned intermediary doctrine with respect to warnings about a prescription drug's properties. Accordingly, for purposes of liability for breach of warranty, "it is the prescribing doctor who in reality stands in the shoes of the ordinary consumer." Carlin, 13 Cal. 4th at 1118 (citation omitted). In other words, the warnings relevant to any breach of warranty

claim are those "directed to the physician rather than the patient." Carlin, 13 Cal. 4th at 1118.

Breach of warranty claims may be maintained against a manufacturer of prescription drugs under a theory of strict liability only when the manufacturer ignores known or knowable defects. As the California Supreme Court has explained,

> a manufacturer of prescription drugs is not strictly liable for injuries caused by such a defect that is neither known nor knowable at the time the drug is distributed. To hold nevertheless that the manufacturer's representation, express or implied, that a drug may be prescribed for a particular condition amounts to a warranty that it is "fit" for and will accomplish the purpose for which it is prescribed, and to allow an action for personal injury for the breach of such warranties, would obviously be incompatible with our determination regarding the scope of a drug manufacturer's liability for product defects.

Brown, 44 Cal. 3d at 1072 (citation omitted). Finally, while privity of contract is ordinarily a prerequisite for recovery on a theory of breach of implied warranties of fitness and merchantability, California recognizes an exception to the privity requirement for cases involving drugs. See Chavez v. Glock, Inc., 144 Cal. Rptr. 3d 326, 353 (Ct. App. 2012).

The SAC alleges that the defendants made six representations to Mr. Utts, his physician, and to the general public through the Eliquis label. The SAC asserts

that Eliquis "does not conform to those representations" because its "serious" side effects include "life-threatening and irreversible bleeding events" like the one suffered by Mr. Utts.[25]

It also brings warranty claims based on two advertising campaigns: one in the period 2013 and 2014, and the second in 2015 and 2016.[26] The SAC alleges that in the

[25] The six representations are that: (1) Eliquis was a "safe and effective" blood thinner without disclosing "the extent of the risk that Eliquis could cause serious bleeding that may be irreversible, permanently disabling, and life-threatening"; (2) that Eliquis was "safe and effective to use without the need for blood monitoring and dose adjustments"; (3) that Eliquis "did not produce any dangerous side effects in excess of those risks associated with other forms of treatment for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation"; (4) that the side effects that Eliquis produces "were accurately reflected in the warnings and that it was accurately [sic] tested;" (5) that Eliquis had been "fully and adequately tested for long-term use and was, inter alia, safe to use in the treatment of atrial fibrillation"; and (6) that Eliquis was "a safer alternative to warfarin and other anti-coagulants." The SAC adds the representation that Eliquis "reduce[s] the risk of recurrence of DVT and/or PE and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery." This indication was not added to the Eliquis label until March 2014. While Mr. Utts was taking Eliquis during this time, he does not claim to have undergone hip or knee replacement surgery or suffered from deep vein thrombosis or a pulmonary embolism. The plaintiffs do not seek to preserve this allegation in their opposition to the motion.

[26] Only those advertisements that were published or aired prior to July 2014 are relevant to the plaintiffs' claims since Mr. Utts suffered his bleeding injury on July 16, 2014.

first campaign the defendants asserted that Eliquis "reduced the risk of stroke more effectively than warfarin," was safer than warfarin, and that, unlike Coumadin, it did not require "blood levels" to be monitored. The SAC asserts that in the second campaign the defendants "portray" Eliquis as the "'best'" treatment for atrial fibrillation and as a better and safer alternative to warfarin. The SAC asserts that these statements were false because Eliquis "is not better than warfarin from a safety perspective."

A. Preemption

The breach of warranty claims are preempted, largely for the reasons already described in connection with the SAC's failure to warn claims. The SAC asserts that the Eliquis labeling did not conform to the representations contained therein because apixaban's serious side effects include excessive bleeding. But, there is no newly acquired information about the risk of bleeding associated with the defendants' particular blood thinner. This risk, which is inherent in a blood thinner, was thoroughly disclosed in the FDA-approved labeling and the plaintiffs' opposition to this motion does not suggest otherwise.

The warranty claims premised on Eliquis' commercial advertising are also preempted. The studies establishing

the superiority of Eliquis to warfarin, at least in certain material respects, were disclosed in the Eliquis label. The literature on which the SAC relies to plead its claims provides no newly acquired information to suggest that the comparisons of the two treatments, which are recited in the labeling and repeated in the commercial advertising, are in any degree false or misleading. Reduced to their essence, the SAC's warranty claims attack a drug manufacturer's right to advertise FDA-approved drugs.

For instance, the SAC alleges that the defendants breached an implied warranty of merchantability that Eliquis was "safe and of merchantable quality" and "fit for the ordinary purposes for which the product was to be used," namely, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The NDA approval process requires the FDA to determine whether a drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" and whether the drug "will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d). In approving Eliquis for manufacture and distribution, the FDA determined that Eliquis was safe and effective for its indicated use, i.e.,

for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Insofar as the plaintiffs' implied warranty claim challenges the FDA's approval of Eliquis for this indication, such claims are preempted.

B. Failure to State a Claim

Many of the assertions in the SAC made in support of the warranty claims are not warranties and do not implicate warranties. For example, there are complaints that the defendants should have disclosed more to physicians about the management of Eliquis patients. Such assertions have already been addressed in connection with the analysis of the failure to warn claims, and need not be addressed further here.

But, even with respect to those portions of the warranty claims that may be said to refer to specific representations or warranties, whether express or implied, the SAC fails to plausibly allege a breach. This is, again, largely for the reasons discussed in connection with the failure to warn claims. One set of "warranties" alleged in the SAC depends on the defendants' assertions that use of Eliquis is accompanied by a risk of excessive bleeding. But, the SAC does not assert that this representation is false. Another set asserts that Eliquis

is safer in several material respects than warfarin. This assertion is made in the Eliquis labeling. For instance, the Eliquis label indicates that "Eliquis was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism" in a trial conducted on patients with nonvalvular atrial fibrillation. None of the literature on which the SAC relies provides a basis to assert that that statement is inaccurate. Indeed, the consensus guide published in the Thrombosis Journal notes generally that apixaban demonstrated a "superior reduction in stroke and systemic embolism, compared to warfarin," and that apixaban resulted in "significantly less major bleeding, compared to warfarin." In sum, there is no basis to find a breach of warranty where the warranty is premised on studies approved by FDA and not otherwise challenged by the secondary literature.

VI. Fraud Causes of Action

The elements of fraud under California law are: (1) the defendant made a false representation; (2) the defendant knew the representation was false at the time it was made; (3) in making the representation, the defendant intended to deceive the plaintiff; (4) the plaintiff justifiably relied on the representation; and (5) the plaintiff suffered resulting damages. West v. JPMorgan

Chase Bank, N.A., 154 Cal. Rptr. 3d 285, 295 (Ct. App. 2013). The elements of negligent misrepresentation mirror those of fraud except for the second element, which for negligent misrepresentation is that the defendant made the representation "without reasonable ground for believing it to be true." Id.

The elements of an action for fraudulent concealment are: (1) the defendant concealed or suppressed a material fact; (2) the defendant had a duty to disclose the fact to the plaintiff; (3) the defendant intentionally concealed the fact with the intent to defraud the plaintiff; (4) the plaintiff was unaware of the fact and would not have acted as he did if he had known of the concealed fact; and (5) as a result of the concealment of the fact, the plaintiff sustained damage. Knox v. Dean, 140 Cal. Rptr. 3d 569, 583 (Ct. App. 2012).

The parties agree that the plaintiffs' fraud, fraudulent concealment, and negligent misrepresentation claims all sound in fraud and are therefore subject to the heightened pleading standards of Rule 9(b). They will be referred to collectively as the fraud claims. The standards for Rule 9(b) pleading are recited above.

The SAC alleges that the defendants engaged in fraudulent concealment and misrepresentations to the FDA,

the medical community, and the public through statements in its December 2012 and March 2014 package inserts, the March 2014 dosing guidelines[27] provided to medical providers (which repeats statements in Eliquis' labeling), and on its website. The contentions concerning the dosing guidelines and package inserts relate to dosage regimens, monitoring, and the lack of a reversal agent. The identified false statements and omissions on the website concern the ARISTOTLE study. The SAC asserts that the defendants "fraudulently submitted" data from the study to the FDA. The negligent misrepresentation claim relies upon the statements made in Eliquis' commercial marketing campaign comparing Eliquis to warfarin that are described above.[28]

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[27] Dosing guidelines constitute labeling. Under the FDCA, "labeling" embraces "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). The Supreme Court has held that the first clause "clearly embraces advertising or descriptive matter that goes with the package in which the articles are transported." Kordel v. United States, 335 U.S. 345, 349-50 (1948). With respect to the second clause, "[o]ne article or thing is accompanied by another when it supplements or explains it . . . . No physical attachment one to the other is necessary." Id. Furthermore, federal regulations define "labeling" to include brochures, booklets, mailings, catalogues, films, sound recordings, and literature "containing drug information supplied by the manufacturer . . . which are disseminated by or on behalf of its manufacturer." 21 C.F.R. § 202.1(l)(2).

[28] The SAC does not indicate with any precision the statements upon which it relies for its negligent misrepresentation claim, but in a footnote in its opposition brief the plaintiffs explain

The SAC summarizes all of these statements as representations that Eliquis "had been tested and was found to be safe and/or effective to reduce the risk of stroke and systemic embolism in patients required to take blood-thinning medications."

A. Preemption

The plaintiffs acknowledge that any fraud claim premised on a theory that the defendants defrauded the FDA is preempted. See Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001). As the Supreme Court explained in Buckman, "[s]tate-law fraud-on-the-FDA claims inevitably conflict with the FDA's responsibility to police fraud consistently with the Administration's judgment and objectives." Id. Recognizing state law fraud-on-the-FDA claims would "cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court," and would, as a result, give applicants an incentive to submit "a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an application." Id. at 351. The plaintiffs request that the SAC's allegations

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that it relies on the statements from the Eliquis marketing campaign that are recited elsewhere in the SAC.

regarding a fraud on the FDA be read merely as evidentiary background to their fraud claims.

It is unnecessary to consider here whether there is any room to allow a fraud claim to proceed when preemption bars the parallel claims brought under other common law theories. See Desiano v. Warner-Lambert & Co., 467 F.3d 85, 95 (2d Cir. 2006) (allowing Michigan fraud claims to proceed when premised on "allegations of wrongdoing apart from the defendant's purported failure to comply with FDA disclosure requirements"). Each of the statements on which the fraud claim is premised depends on statements made to and approved by the FDA. There is no newly acquired information that required or suggested that the allegedly fraudulent statements should be altered to remain truthful and non-fraudulent. Accordingly, the fraud claims are preempted.

B. Failure to State a Claim

The defendants have also shown that the three fraud claims must be dismissed for failure to state a claim. The SAC fails to plead with the particularity required by Rule 9(b) a plausible claim of fraud in connection with any of the statements it identifies.

1. Dosing Guidelines

The SAC alleges that the March 2014 dosing guidelines contain two fraudulent statements.[29] First, the guidelines state: "[n]o dose adjustment required in patients with mild, moderate, or severe renal impairment alone." According to the plaintiffs, this statement "intentionally misled prescribing physicians and consumers to believe that even with moderate or severe renal impairment, Eliquis was safe, when in fact, it was not appropriate for such patients."[30] Second, the guidelines state that Eliquis "[d]oes not require routine monitoring using international normalized ratio[] (INR) or other tests of coagulation." The SAC alleges that "given the extreme bleeding risk in patient populations (some of which were not adequately studied), monitoring is required for some or all patient populations, as the EMA and FDA have been suggesting."

These allegations are iterations of the dosage and monitoring allegations discussed above. The dosage guidance provided in the dosing guidelines was approved by the FDA as

[29] The SAC makes a third incomplete allegation: "While there is a section [in the dosing guidelines] regarding the fact that 'there is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose,' there is no."

[30] The SAC does not assert that Mr. Utts suffered from any renal impairment, and therefore, does not provide a basis to assert that he was defrauded by this statement.

part of its review of Eliquis' labeling. The SAC identifies no studies or secondary literature to suggest that the guidance was flawed, much less that it is fraudulent. Moreover, the SAC identifies no support for its assertions that Eliquis is not safe for patients with renal impairments, or that any particular undisclosed monitoring regimen is required for patients for whom Eliquis has been prescribed.

2. Package Inserts

The allegations regarding the package inserts are more cryptic. The SAC does not identify any particular allegedly defective language in the inserts. Instead, the SAC first asserts that the recommended dosage in the insert "is false" because "the patient characteristics . . . should have been limited to one characteristic, instead of two of the listed characteristics." Second, the SAC asserts that the defendants "withheld information and data that without the reversal agent, death could result."

For the reasons recited earlier in this Opinion, the SAC fails to plead a claim regarding dosage. That is even more true with respect to the fraud claims, where the SAC completely fails to meet the Rule 9(b) particularity burden. The reference to patient characteristics appears to be a reference to the label's recommendation that the daily dosage of 5 mg twice daily be cut in half for patients that have two of three identified

characteristics.[31] Nothing in the SAC or the documents integral to it provide any plausible basis to assert that scientifically reliable information might be available to support the change requested in the SAC, that is, that the dosage be reduced when only one of the three characteristics is present.

Nor can the SAC credibly assert that the package inserts withheld information concerning the potentially fatal adverse effects of Eliquis. Rather, the label states in clear, unambiguous terms that Eliquis "can cause serious, potentially fatal, bleeding" and that no antidote exists.

3. Eliquis Website

The SAC identifies three allegedly fraudulent statements regarding the ARISTOTLE study that appeared on the Eliquis website: (1) "For patients with Nonvalvular Atrial Fibrillation (NVAF), Eliquis was proven effective in 2 Phase III studies"; (2) "ELIQUIS is the ONLY anticoagulant that demonstrated superiority in BOTH stroke/systemic embolism and major bleeding vs warfarin"; and (3) "Eliquis had less major bleeding than warfarin" and that "unlike warfarin," no routine monitoring is required. The SAC explains that "[a]ll of this data was fraudulently submitted to the FDA, and then Defendants used this

[31] The three characteristics are: (1) the patient is 80 years or older; (2) the patient weighs 60 kg or less; or (3) the patient has serum creatinine levels of 1.5 mg/dL or more.

fraudulent data to misrepresent the effectiveness of Eliquis when citing to the ARISTOTLE study in support of its claims of the medication's efficacy."

The SAC and documents integral to it indicate that the FDA approved Eliquis after examining the ARISTOTLE study and evaluating its flaws. Moreover, while the SAC and the secondary literature on which the SAC relies include discussions and critiques of the ARISTOTLE study, neither the SAC nor that literature provides a basis to plausibly plead that any of the website statements is fraudulent. Conclusory assertions of fraud are not sufficient.

4. Eliquis Marketing Campaign

As explained in the plaintiffs' opposition to this motion, the SAC's negligent misrepresentation cause of action is premised on comparisons between apixaban and warfarin made in the defendants' marketing campaigns. These comparisons are described above.

The SAC's descriptions of Eliquis' direct-to-consumer advertisements fail to meet Rule 9(b)'s heightened pleading standard. The SAC merely paraphrases the assertions made in Eliquis' television advertisements without providing the exact content of the statements. Moreover, the plaintiffs do not plausibly allege that these representations were false. For example, none of the data or studies cited in the SAC contradict

the information contained in these advertisements. As explained above, not a single report, study, or article cited in the SAC disproves the defendants' claims that: (1) Eliquis reduces the risk of stroke more effectively than warfarin; (2) Eliquis is safer than warfarin; and (3) Eliquis patients' blood levels do not need to be monitored.

VII. California Consumer Protection Claims

The plaintiffs allege that the defendants violated California's Unfair Competition Law ("UCL"), Cal. Bus. & Prof. Code § 17200, et seq., California's False Advertising Law ("FAL"), Cal. Bus. & Prof. Code § 17500, et seq., and California's Consumers Legal Remedies Act ("CLRA"), Cal. Civ. Code § 1750, et seq. To the extent these consumer protection claims are premised on allegations of fraudulent conduct, they must be pleaded with particularity under Rule 9(b), Fed. R. Civ. P.

California's UCL prohibits any "unlawful, unfair or fraudulent business act or practice and unfair, deceptive, untrue or misleading advertising." Cal. Bus. & Prof. Code § 17200. Each of the three prongs of the UCL -- "unlawful," "unfair," and "fraudulent" -- provides an "independent basis for relief." South Bay Chevrolet v. General Motors Acceptance Corp., 85 Cal. Rptr. 2d 301, 316 (Ct. App. 1999) (citation omitted). The UCL "'borrows' violations from other laws by

making them independently actionable as unfair competitive practices." Korea Supply Co. v. Lockheed Martin Corp., 29 Cal. 4th 1134, 1143 (2003). For example, "any violation of the false advertising law necessarily violates the UCL." Kasky v. Nike, Inc., 27 Cal. 4th 939, 950 (2002) (citation omitted).

The FAL, in turn, "prohibits the dissemination in any advertising media of any 'statement' . . . 'which is untrue or misleading, and which is known, or which by the exercise of reasonable care should be known, to be untrue or misleading.'" Hambrick v. Healthcare Partners Med. Grp., Inc., 189 Cal. Rptr. 3d 31, 54 (Ct. App. 2015) (citing Cal. Bus. & Prof. Code. § 17500). In sum, "[f]alse advertising under the FAL constitutes a fraudulent business practice under the UCL." Id.

The CLRA prohibits specified "unfair methods of competition and unfair or deceptive acts or practices." Cal. Civ. Code § 1770(a). Prohibited practices include: "[r]epresenting that goods or services have . . . characteristics, ingredients, uses [or] benefits . . . that they do not have"; "[r]epresenting that goods . . . are of a particular standard, quality, or grade . . . if they are of another"; and "[a]dvertising goods or services with intent not to sell them as advertised." Cal. Civ. Code § 1770(a)(5), (7), and (9). The list of proscribed practices in the CLRA also encompasses the "concealment or suppression of

material facts." McAdams v. Monier, Inc., 105 Cal. Rptr. 3d 704, 711 (Ct. App. 2010).

In an action for false advertising under California's consumer protection laws, the plaintiff "bears the burden of proving the defendant's advertising claim is false or misleading." Nat'l Council Against Health Fraud, Inc. v. King Bio Pharm., Inc., 133 Cal. Rptr. 2d 207, 211 (Ct. App. 2003). Because the UCL and FAL prohibit not only advertising which is false, but also advertising which is "misleading," it is necessary only to show that "members of the public are likely to be deceived." Chapman v. Skype Inc., 162 Cal. Rptr. 3d 864, 871 (Ct. App. 2013) (citation omitted). "This is determined by considering a reasonable consumer who is neither the most vigilant and suspicious of advertising claims nor the most unwary and unsophisticated, but instead is the ordinary consumer within the target population." Id. at 871-72 (citation omitted). Furthermore, "likely to deceive" implies "more than a mere possibility that the advertisement might conceivably be misunderstood by some few consumers viewing it in an unreasonable manner." Id. at 872 (citation omitted). Rather, the advertisement must be such that "a significant portion of the general consuming public or of targeted consumers, acting reasonably in the circumstances, could be misled." Id. (citation omitted). Whether consumers are likely to be deceived

is a question of fact that can be decided on a motion to dismiss "only if the facts alleged in the complaint, and facts judicially noticed, compel the conclusion as a matter of law that consumers are not likely to be deceived."[32] Id.

The SAC brings a single cause of action premised on a violation of the three California consumer protection laws. The claim incorporates by reference the SAC's prior allegations regarding the defendants' "marketing and advertising" campaign, asserting that the defendants failed to disclose the dangerous side effects of Eliquis and misrepresented its benefits to physicians and consumers.

For the reasons already explained, the plaintiffs' consumer protection claims are preempted and fail as well to meet the pleading standards under Rules 8(a) and 9(b), Fed. R. Civ. P.[33] The SAC provides a threadbare recital of the elements of California's consumer protection laws, supported by mere

[32] The parties do not address whether the learned intermediary doctrine applies to claims brought under California's consumer protection laws. See Saavedra v. Eli Lilly & Co., 2:12-cv-9366-SVW-MAN, 2013 WL 3148923, at *2-4 (C.D. Cal. June 13, 2013) (finding that the learned intermediary doctrine applies to consumer protection claims predicated on a failure to warn).

[33] To the extent the SAC's consumer protection claims are lack of substantiation claims, there does not appear to be a private right of action under California law. See King Bio, 133 Cal. Rptr. 2d at 213 ("Private plaintiffs are not authorized to demand substantiation for advertising claims.").

conclusory statements. The SAC does not allege with any specificity the contents of the fraudulent advertisements, when such representations were made, and why such representations were, at the very least, misleading to a reasonable consumer. Nor does the SAC plausibly allege that there exists certain information or data that somehow undermines or contradicts the information communicated through Eliquis' advertising campaign. Accordingly, the plaintiffs' consumer protection claims are dismissed since they cannot plausibly allege that the defendants' advertising contained false or even misleading representations.

VIII. Strict Liability, Negligence, and Gross Negligence

The parties principally discuss strict liability and negligence theories in the context of other claims which have already been addressed in this Opinion. The plaintiffs have identified no separate reason to believe that these claims would survive the present motion if the other claims cannot. Nor do the plaintiffs describe precisely in what ways the defendants negligently failed to warn of certain risks or advertised Eliquis other than those already described.[34]

[34] Because none of the plaintiffs' claims survives the defendants' motion to dismiss, the plaintiffs' claims for loss of consortium and punitive damages are dismissed as well and need not be addressed.

CONCLUSION

The defendants' March 10, 2017 motion to dismiss the Second Amended Complaint is granted in its entirety. The Clerk of Court shall enter judgment for the defendants.

Dated: New York, New York
May 8, 2017

DENISE COTE
United States District Judge