UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PLAVIX MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (NO. II)	MDL No. 2418
This Document Relates to: ALL CASES	Docket No.: 3:13-cv-04518-FLW-TJB

PLAINTIFF'S BRIEF IN OPPOSITION TO
DEFENDANTS' OMNIBUS MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

. Plaintiffs respectfully request that this Court deny *Defendants' Omnibus Motion for Summary Judgment as to All Remaining Plaintiffs*. Generally speaking, Defendants ask this Court to find Plaintiffs' claims preempted pursuant to *Wyeth v. Levine*. However, as will be shown below, there are fact based questions that remain. Summary Judgment is not an appropriate remedy here, especially with the considerable volume of Changes Being Effected data that the Defendants make no effort to address. Thus, for all the reasons below, Defendants' Motion for Summary Judgment should be denied.

STATEMENT OF FACTS

Moving Defendants are the manufacturers and distributors of the antiplatelet drug clopidogrel, sold under the brand name Plavix. Plavix was first approved by the FDA in November 1997. The FDA approval of Plavix was based entirely on a single study, known as CAPRIE, which compared the relative efficacy of Plavix and aspirin.[1] Specifically, CAPRIE studied the effectiveness of Plavix versus aspirin in preventing vascular events, such as heart attacks and strokes, in three distinct patient groups: patients with established peripheral artery disease ("PAD"), patients with recent ischemic stroke, and patients with recent heart attack.[2] When all patients across all three patient types were viewed together in a combined endpoint, Plavix was 8.7% more effective than aspirin.[3] However, an analysis of each subgroup was also done, which showed that the 8.7% figure cited in the study's conclusion did not apply to the majority of patients.[4] For example, for patients with heart attack, Plavix was found to be 3.7%

[1] Ex. A (CAPRIE study); Ex. B (FDA warning letter of 12/11/1997).
[2] *Id.*
[3] *Id.*
[4] *See id.*

less effective.[5] For patients with stroke, Plavix was found to be 7.3% more effective than aspirin, but unlike the reported 8.7% figure, this finding was not "statistically significant."[6]

Nevertheless, Defendants launched a misleading advertising scheme for Plavix, touting it as 8.7% more effective than aspirin across the board for all patient types, drawing an admonishment from the FDA.[7] In a letter to one of the manufacturers of Plavix, the FDA informed Defendants that it considered any advertisement claiming that Plavix was 8.7% more effective than aspirin to be false and/or misleading, unless such a claim was accompanied by contextual information.[8] Although the specific FDA letter used in the deposition in this case was in response to specific promotional materials, the FDA also objected to *any* superiority claim of Plavix over aspirin, in multiple documents – both before and after Plavix was approved.[9] Yet Defendants ignored the FDA's admonishments and persisted with their scheme – and it worked.

Based on CAPRIE, the Defendants promoted Plavix as being safer and causing fewer gastrointestinal bleeding complications than aspirin, even though the study results showed a negligible difference in bleeding risk when compared to aspirin, a drug that carried a warning about bleeding in the Warnings Section of its label.[10] Contrary to Defendants' assertions, no study exists that justifies Defendants' decision to denigrate bleeding information to the "Precautions" section of the label. Throughout the relevant time period, Plavix remained the only drug in its class to not feature bleeding in the "Warnings" section.[11] Defendants have not pointed to any evidence of why they thought bleeding risk information did not need to be in the

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[5] *Id.*
[6] *See id*.
[7] Ex. B (FDA warning letter of 12/11/1997).
[8] *See id.*
[9] *Id*.
[10] *See* Ex. C (*Chan* study at 239); *see also* Ex. A (CAPRIE study).
[11] *See* Ex. D (Aspirin label); Ex. E (Effient Label); Ex. F (Brilinta label).

"Warnings" section; therefore, Plaintiffs and this Court can only surmise that Defendants consciously sought to diminish the significance of the risk of bleeding with Plavix in order to gain a competitive advantage over other drugs – no other rationale for maintaining an inferior warning to comparable drugs is forthcoming. Furthermore, Defendants' decision to refuse to put bleeding information in the "Warnings" section was contrary to the opinions of their own scientists – BMS scientist Mel Blumenthal opined as early as 2004 that the lack of information about bleeding in the "Warnings" section rendered Plavix's label "weak."[12] Nevertheless, Defendants never even attempted, despite the weight of post-approval data, to modify their label so as to feature bleeding information in the "Warnings" section.

LEGAL STANDARD

Summary judgment is inappropriate unless the movant can show both that there is no genuine issue of material fact, and that, viewing the facts in the light most favorable to the non-movant, movant is entitled to judgment as a matter of law. *Mattson v. Bristol-Myers Squibb Co.*, 2013 U.S. Dist. LEXIS 58563 at *9 (D.N.J. Apr. 22, 2013); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986); Fed. R. Civ. P. 56(c). A genuine issue of fact exists wherever there is "a sufficient evidentiary basis on which a reasonable jury could find for the non-moving party." *Mattson*, 2013 U.S. Dist. LEXIS 58563 at *9 (quoting *Kaucher v. County of Bucks*, 455 F.3d 418, 423 (3d Cir. 2006)); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). In determining whether an issue of fact is genuine, a court must view the facts and all reasonable inferences drawn therefrom in the light most favorable to the nonmovant. *Mattson*, 2013 U.S. Dist. LEXIS 58563 at *9; *Matsushita Electrical Industrial Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986).

[12] *See* Ex. G (Blumenthal email) ("The current US Plavix labeling has nothing about bleeding in the 'Warnings' section, and the wording in the 'Precautions' section is relatively weak…").

Initially, the moving party bears the burden of showing the absence of any genuine dispute of material fact. *Mattson*, 2013 U.S. Dist. LEXIS 58563 at *10; *Celotex*, 477 U.S. at 323. Only after the movant has adduced sufficient evidence to make this showing does nonmovant bear the burden of adducing evidence to contradict the movant's. *Id.* At summary judgment, the court's role is not to evaluate the evidence and decide the truth of the matter, but only to determine whether a genuine dispute of fact exists for trial. *Mattson*, 2013 U.S. Dist. LEXIS 58563 at *11; *Anderson*, 477 U.S. at 249.

At the outset, Plaintiffs note that there is a well-established presumption against preemption, because preemption always raises significant federalism concerns by upsetting the balance of power between state and federal governments as coequal sovereigns. *See Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 449 (2005). Courts typically refrain from invalidating state law on preemption grounds unless a defendant can overcome the considerable burden of proving that such was the "clear and manifest purpose of Congress." *Altria Group, Inc. v. Good*, 555 U.S. 70, 77 (2008); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996). The presumption is particularly strong in the tort context, as states have traditionally enjoyed broad police powers to regulate issues pertaining to the health and safety of their citizens. *See Lohr*, 518 U.S. at 485; *Bruesewitz v. Wyeth, Inc.*, 561 F.3d 233, 240 (3d Cir. 2009) (citing *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008). Indeed, the Supreme Court has declared that "pre-emption is a demanding defense." *Wyeth v. Levine*, 555 U.S. 555, 573 (2009). The burden is squarely on the defendant drug manufacturer to prove that it applies. *See id.*

The Supreme Court has ruled unambiguously that, in the context of pharmaceuticals litigation, most state law failure-to-warn claims are not preempted. *See Levine*, 555 U.S. at 570-71. The Court has declared that, in enacting the federal regulatory scheme, Congress had the

intent that drug companies – not the FDA – would bear ultimate responsibility for ensuring that their products bear adequate warnings about the risks they pose. *See id.* Although the FDA generally must approve the warnings that companies apply to their products, the Supreme Court has interpreted the FDA's "Changes Being Effected" ("CBE") regulation as permitting the manufacturers broad discretion to unilaterally *strengthen* the warnings pertaining to a drug without FDA pre-approval, so long as the change is based on "newly acquired information." *See id.* at 568*; see also* 21 C.F.R. § 314.70(c)(6)(iii)(A) (the CBE regulation). As the Supreme Court has explained, such "newly acquired information" is not restricted to new data never before submitted to FDA: the term also applies to new analyses of old data. *Levine*, 555 U.S. at 569. Furthermore, the Court noted that it is not necessary that any such new analysis had actually been completed; preemption is inappropriate even if the drug manufacturer merely "could have analyzed [] accumulating data." *See id.* at 570. Although the FDA maintains the discretion to reject a warning added or strengthened under the CBE regulation, absent "clear evidence" that FDA would have done so, a defendant cannot rely on this possibility to establish a preemption defense. *See id.* at 571-73.

ARGUMENT

I. PLAINTIFFS' FAILURE-TO-WARN CLAIMS ARE NOT PREEMPTED

Defendants argue that all of Plaintiffs' claims are pre-empted under the doctrine of impossibility preemption. Specifically, Defendants contend that it would have been impossible for them to comply with their Delaware state-law duty to adequately warn of the dangers of Plavix without violating FDA regulations. For the following reasons, Defendants could have and, in fact, were required to, satisfy their duty under both state and federal law. Consequently, Plaintiffs' claims are not preempted.

A. Failure-to-Warn Claims Based on Information that Existed at the Time of Initial Approval Are Not Automatically Preempted.

The primary thrust of Defendants argument is that, to the extent Plaintiffs' claims criticize information that was in Plavix's label at the time of initial approval, those claims are preempted, and therefore, all claims are pre-empted, even post-approval claims. This incorrect statement of law flies in the face of both Supreme Court and Third Circuit precedent. Accordingly, Defendants' claim of impossibility preemption must fail.

Defendants are incorrect in asserting that failure-to-warn claims premised on information that existed at the time of initial approval are automatically preempted. Throughout their brief, Defendants criticize Plaintiffs' general labeling expert, Dr. Randall Tackett, for his opinion that the Plavix label was inadequate "from the get go." *See Def Brief* at 2. These comments, according to Defendants, require a finding of preemption as to *all* of Plaintiffs' claims, because, as they argue, all failure-to-warn claims based on information existing at the time of a drug's initial approval are preempted. *See Def Brief* at 16. To support this proposition, Defendants cite only to two non-controlling decisions from sister circuits: *Celexa* and *Utts*. However, Defendants' interpretation of these cases flies in the face of established law, both at the Supreme Court level and in this circuit. As such, Defendants' arguments are unavailing.

The seminal Supreme Court decision on impossibility preemption in the pharmaceutical context is *Wyeth v. Levine*, 555 U.S. 555 (2009). The *Levine* case concerned the drug Phenergan, which when administered by a particular method could cause gangrene and loss of limb. *Id.*, at 559. The record in that case reflected that, at one point in time, the FDA had considered data suggesting that Phenergan could cause gangrene, but instructed Wyeth, the manufacturer to

maintain labeling for Phenergan that contained no warning of this risk.[13] *Id.* at 561-62. Wyeth argued that it could not have thereafter added a warning about gangrene under the CBE regulation, as it had no "newly acquired information" suggesting that Phenergan caused the condition. *Id.* at 568-69. However, the Supreme Court soundly rejected this argument, holding that Wyeth could meet the "newly acquired information" standard under the CBE by re-analyzing information previously submitted to the FDA in light of continuing reports of gangrene. *Id.* at 569-70. Despite the fact that the revisions to Phenergan's label allegedly required by state law were based on information previously considered and rejected by FDA, the Court found that plaintiff's claims were not preempted.[14] *Id.* at 573.

Similarly, the jurisprudence of this Circuit also permits plaintiffs to premise a failure-to-warn claim on deficiencies in a drug's labeling that were previously approved by FDA. In *In re Fosamax Alendronate Sodium Products Liability Litigation*, 852 F.3d 268 (3d Cir. 2017), the Third Circuit found against preemption, despite the fact that FDA had previously considered and in fact *explicitly rejected* the addition of a warning about atypical femoral fractures to Fosamax's label. *See In re Fosamax Alendronate Sodium Products Liability Litigation*, 852 F.3d 268 (3d Cir. 2017).

The record in *Fosamax* revealed that FDA was informed about Fosamax's potential to cause atypical femoral fractures as early as 1992; however, when it approved Fosamax in 1995,

[13] Specifically, the record reflected that, in 1987, the FDA had suggested that Wyeth add a warning about gangrene to Phenergan's label, but ignored a proposed label submitted by Wyeth in 1988 that did so. *Levine*, 555 U.S. at 561-62. Many years later, in 1996, FDA again reviewed Phenergan's label, which still included no warning of gangrene, and instructed Wyeth to maintain its current form. *Id.* Plaintiff in that case claimed that

[14] It is important to note that, while *Levine* is technically a "post-approval" case in that the record did not reflect that concerns about gangrene had arisen at the time of Phenergan's initial approval in 1955, the situation it presents is factually analogous to a "pre-approval" case. In *Levine*, FDA had considered data regarding gangrene for the specific purpose of deciding whether to include a warning in regard thereto in Phenergan's label, but ultimately opted to approve a label that did not include one. *See Levine*, 555 U.S. at 561-62. Nevertheless, the Court found no preemption. *Id.* at 573. Similarly, in the instant case, FDA considered bleeding information from CAPRIE before initial approval, but approved a label in which that information was not included in the "Warnings" Section. Despite Defendants' assertion of a pre/post-approval "dichotomy," they have provided no evidence of such in Supreme Court precedent.

FDA required no warning to doctors about this potential side effect.[15] *Id.* at 275. Despite this evidence, the *Fosamax* court rejected defendant's claim of impossibility preemption. *Id.* at 300. The court recognized that, at summary judgment, a defendant manufacturer bears the burden of establishing that it *could not* have unilaterally strengthened its drug labeling, either because the CBE process was unavailable, or because there was "clear evidence" that the FDA would reject a CBE amendment. *Id.* at 295. Indeed, it is worth repeating: it is not Plaintiffs' burden to prove that Defendants *could* have utilized the CBE regulation to amend the Plavix label; Defendants must show that no label change was possible, which they have failed to do here. *See id.*

Defendants have not even attempted to meet their burden under *Levine* and *Fosamax*. As stated above, at summary judgment, Defendants carry the burden of affirmatively proving the elements of their preemption defense. *See Fosamax*, 852 F.3d at 271. To do so, Defendants *must* show either that they would not be permitted to effect a unilateral change under the CBE regulation, or that, had they done so, FDA would have exercised its discretion to reject such a change. *See Levine*, 555 U.S. at 568-71.

As will be shown below, Defendants have not proven *either* of these possible elements. Defendants merely indicate that they could not utilize the CBE process *prior* to initial approval, which they hope will be enough to convince this Court to deviate from the established precedents of *Levine* and *In Re: Fosamax. See Def Brief* at 18. However, Defendants have made no attempt to explain why they made no effort to strengthen their warnings under the CBE process in the 20 years *following* initial approval. They do not even affirmatively claim that no new information

[15] Defendants puzzlingly refer to *Fosamax* as a "post-approval" case, despite the clear evidence that FDA had received and considered data regarding the possibility of atypical femoral fractures before Fosamax was approved. *See Def. Brief* at 17. This is perhaps due to the *Fosamax* court's more extensive treatment of whether a subsequent, post-approval FDA decision amounted to "clear evidence" that FDA would reject a CBE submission adding such a warning. However, the fact remains that the court did not consider the fact that FDA knew about this side effect before approval to automatically trigger preemption, as Defendants invite this Court to do.

arose which would have justified a CBE amendment, a claim which Plaintiffs nevertheless disprove below. Consequently, Defendants are required to provide "clear evidence" that the FDA would have rejected a change to the Plavix label made under the CBE. *See Fosamax*, 852 F.3d at 284-86 (citing *Levine*, 555 U.S. at 571). Defendants have made no such claim.[16] As such, Defendants' motion falls *well* below the applicable standard under relevant precedent. Defendants have not even attempted to carry their summary judgment burden, and their motion must therefore be denied.

B. The Precedents Cited by Defendants do not Apply here.

Defendants' *lone* argument here is that "pre-approval" cases—meaning cases whose claims are premised upon data that was known to FDA before the time of approval—are automatically preempted, and by proxy, the claims herein are preempted. To this end, they cite two non-controlling cases from other circuits – *In re Celexa* and *Utts v. Bristol Meyers Squibb*. Neither of these precedents is applicable here, as Defendants' interpretation of both of these decisions invert the burden of proof established by *Levine* and *Fosamax*.

For example, in *In re Celexa & Lexapro Marketing & Sales Practices Litigation*, 779 F.3d 34, 43 (1st Cir. 2015), the First Circuit dismissed plaintiff's claims as preempted, on the basis that the complaint had failed state sufficient facts to defeat a preemption defense. *Id.* The First Circuit noted that, although the complaint alleged problems with the studies behind FDA approval, it did not allege the existence of any new information that would have permitted the defendants to change their labels using the CBE regulation, nor did it allege that FDA was

[16] Even if Defendants *had* claimed that FDA would have rejected a label change made under the CBE regulation, such an argument would be untenable. In *Fosamax*, the record reflected that the defendant manufacturer had affirmatively approached FDA and requested the label change that plaintiffs alleged was required, only to be denied. *Fosamax*, 852 F.3d at 298-99. However, the *Fosamax* court *still* found that defendant had not met its burden, noting that a reasonable juror could conclude that FDA merely disagreed with defendant's *wording* of the proposed label. *See id.* Here, Defendants cannot even point to evidence that they ever proposed an adequate label to FDA, let alone that FDA rejected it. As such, it is not possible for Defendants to prove up this essential element of their defense.

unaware of the supposed manipulation of the initiation studies. *See id.* However, as this is a motion for summary judgment, rather than a motion to dismiss, the relevance of *Celexa* to Defendants' arguments is unclear.[17]

To the extent that Defendants attempt to suggest that the *Celexa* court shifted the *summary judgment* burden onto plaintiffs to prove that defendants could have used the CBE regulation to strengthen their warning, their interpretation flies *directly* in the face of not only F.R.C.P. 56, but also the *Levine* and *Fosamax* decisions. It is Defendants' burden as movant to establish the elements of their preemption defense. *Fosamax*, 852 F.3d at 295; *see also* Fed. R. Civ. Pro. 56. As such, Defendants' invitation to interpret *Celexa* so as to invert the burden of proof at summary judgment should be summarily rejected.

The only other matter cited in support of its arguments is *Utts v. Bristol-Myers Squibb*, 226 F. Supp. 3d 166 (S.D.N.Y.2016), a pair of non-binding decisions out of the Southern District of New York. In *Utts*, as in *Celexa*, plaintiffs' complaint was dismissed because it "[did] not appear to be premised on any information that … might constitute 'newly acquired information' under the CBE regulation." *Id*. at 184. As Defendants indicate, the *Utts* court claimed that, "read holistically," Supreme Court precedent establishes that "federal law preempts all pre-FDA approval failure to warn … claims." *Id.* at 178.

The *Utts* precedent is an outlier, and the facts of that decision have little to do with the facts of the instant litigation. *Utts* involved a prescription blood thinner, Eliquis, which was the

[17] The complaint in the instant case is replete with allegations of new information for purposes of the CBE, discussed below. Tellingly, Defendants did not make a Motion to Dismiss based on the ruling in *Celexa* in this case. Plaintiffs interpret this as a tacit admission that Plaintiffs' complaints did not have any of the deficiencies identified in that case.

cause of a severe bleeding injury experienced by the Plaintiff. *Id.* at 172-73. But that is the end of any similarity between this litigation and the *Utts* decision.

First, *Utts* involves a 12(b)(6) motion to dismiss, rather than a motion for summary judgment. *Id.* at 173. Second, the drug involved in *Utts*, Eliquis, had a warning label that acknowledged the potential for an unstoppable bleeding event, which the Court found adequate. *See Utts II*, 2017 U.S. Dist. LEXIS 70317, at *57 (S.D.N.Y. May 8, 2017).

To that point, the Southern District of New York also determined that preemption, even in the face of the "clear evidence" standard of *Wyeth v. Levine*[18], was appropriate during the pleading phase of the litigation, because the Plaintiffs were unable (without having taken any discovery) to plead any "newly acquired information" in their complaint. *Utts II*, at 2017 U.S. Dist. LEXIS 70317, at *30-53 (discussing the various pieces of newly acquired data pled by Plaintiffs in *Utts II*, and still finding reason to dismiss the matter as preempted.)

[18] Several other Courts, who were presented with the same arguments as the Southern District of New York was in *Utts*, soundly rejected them for the backwards application of the "clear evidence" standard of *Wyeth v. Levine* they called for. *See In re: Zofran (Ondansetron) Products Liability Litigation*, 2016 WL 287056, at *3 (D. Mass. Jan. 22, 2016) (denying a motion to dismiss and noting "the relevant standard under *Levine* uses the phrase 'clear evidence.' Whatever the contours, in this context, of the word 'evidence,' it surely contemplates some form of fact-based evaluation. The Court is reluctant to issue a ruling on a motion to dismiss without giving the plaintiffs some opportunity to develop the facts. . . ."); *see also Koho v. Forest Labs., Inc.*, 17 F. Supp. 3d 1109, 1118 (W.D. Wash. 2014) ("[T]he clear evidence standard is a fact based inquiry that depends on the express type of warning at issue and the particular facts of each case"); *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1270 (W.D. Ok. 2011) (explaining that ascertaining conflict preemption is "necessarily fact specific").

The *Utts* decision references the standard set forth in *Levine*, but then seemingly proceeds to ignore it, on the basis that the Supreme Court "focused exclusively on what a drug manufacturer could do post-approval." *Id.* at 180. However, the court does not define how precisely such a pre/post-approval dichotomy works.

Taken to its logical conclusion, the rationale of *Utts* and *Utts II* is thus: (1) no claim based on pre-approval data can survive preemption, and (2) without some kind of post-approval FDA study or recall of the product, all claims are preempted at the pleading phase. That is not what the Supreme Court intended when it handed down *Levine*, and that is not what the Third Circuit held in *In re Fosamax*. If the court meant to say that no claim premised on data that was submitted to FDA prior to approval can escape preemption, as Defendants suggest, then it is completely at odds with both Supreme Court and Third Circuit precedent.[19]

Defendants cannot point to a single case in this Circuit or anywhere that concurs with this reading of *Utts*, as none exist. If instead the *Utts* court meant to say, like the *Celexa* court, that the plaintiff had not pled any allegations that could support the possible existence of "newly acquired information," then it, too, is completely inapplicable to the instant case.[20] Either way, Defendants' arguments that no failure-to-warn argument touching on information that existed prior to approval are without legal support, and their motion should be denied.

II. DEFENDANTS HAD SUFFICIENT POST-APPROVAL INFORMATION TO STRENGTHEN PLAVIX'S WARNINGS UNDER THE CBE REGULATIONS.

[19] For example, in *Fosamax*, the court refused to find preemption even though the FDA had been aware of the link between Fosamax and atypical stress fractures since before it approved the drug. *See* 852 F.3d at 296. In *Levine*, the court held that defendant could have used the CBE regulation to change Phenergan's label, because it "could have" re-analyzed data previously submitted to and examined by FDA. 555 U.S. at 569-70.

[20] Plaintiffs note that, although the *Utts* complaint alleged that an accumulation of adverse events observed in patients on Eliquis constituted "newly acquired information," the court faulted this allegation as "threadbare." *See* 226 F. Supp. 3d at 185. Presumably, the court was dismissing the complaint based on the insufficiency of this assertion, *not* on the basis that even a well-pled allegation of new information would fail in a "pre-approval" case.

Defendants argue that Plaintiffs' claim that Defendants understated the bleeding risks of Plavix in their label is preempted, because FDA knew that bleeding was a side effect of Plavix before approving Plavix. But this is a tremendous oversimplification of the issue at bar. Indeed, Defendants ignore the substantial evidence and numerous *post-approval* studies that would have enabled them to make a change to their label. They have failed to meet their burden or even properly reference the elements of their preemption defense. As will be shown below, the Defendants have failed to show the "clear evidence" required to establish the affirmative defense of preemption.

Defendants fail to meet their burden to establish a defense of impossibility preemption, because the record is replete with evidence that "newly acquired information" was available about the bleeding risks of Plavix, which enabled Defendants to unilaterally change Plavix's label under the CBE regulation, but Defendants still took no such action.

The FDCA defines "Newly Acquired Information" as:

> Data, analyses, or other information not previously submitted to the [FDA], which may include (but are 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, event, or analyses reveal risks of a different type or greater severity or frequency upon previously included in submissions to the FDA.

21 C.F.R. § 314.3(b)(*emphasis added*).

Thus, a manufacturer may unilaterally change its label to reflect Newly Acquired Information "[t]o add or strengthen a contraindication, warning, precaution or adverse reaction . . . [t]o add or strengthen a statement about overdosage . . . or [t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." 21 C.F.R. § 314.70(c)(6)(iii)(A)(B)(C). If a manufacturer uses a CBE supplement to add or

strengthen a warning, and/or precaution, there must be reasonable evidence of a causal association. 73 Fed. Reg. 49603 (*citing* 21 C.F.R. § 201.57(c)(6)).

"Agency guidance clarifies that 'reasonable' evidence' is 'a standard that could be met by a wide range of evidence,' including evidence that 'would not also support a higher evidentiary standard, such as a finding that there is a "preponderance" of evidence that a product actually causes a particular kind of adverse event.'" *In re Fosamax*, 852 F.3d at 291-292 (*quoting* 73 Fed. Reg. 49603, 49604). As for adding or strengthening the adverse reaction section, there must be "some basis to believe there is a causal relationship." 21 C.F.R. § 201.57(c)(7); 73 Fed. Reg. 49603.

The Supreme Court has ruled that, if a drug company could have used the CBE regulation to unilaterally change a drug's label to reflect the information that state law requires it to include, there can be no preemption. *See Levine*, 555 U.S. at 568-73; *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011). However, the Supreme Court has clarified that "newly acquired information" does not require newly acquired data – a new or different analysis of old data also suffices. *See Levine*, 555 U.S. at 569.

Plaintiffs claim that Plavix's label was inadequate, because the placement of risk information about bleeding outside the "Warnings" section minimized the severity of those risks. *See* Ex. H (Report of Dr. Tackett, at ¶ 192). The record shows that the Defendants had multiple opportunities, and were presented with numerous studies, to make use of the CBE regulation to correct this inadequacy after Plavix's initial approval – both due to data recovered from post-approval studies, and to the accumulation of post-marketing data.[21] As a result, Defendants'

[21] Applicable precedent evidences that the standard for proving that the CBE regulation was not available is a demanding one. In *Fosamax*, the court noted that FDA regulations require only "'reasonable evidence' of a causal association" to add a warning to the "Warnings" section of a drug label. 852 F.3d at 297-98 & n. 154 (citing 73 Fed.

claim of preemption must fail absent clear evidence that FDA would have rejected changes made under the CBE regulation, evidence that Defendants cannot provide. *See In re Fosamax*, 852 F.3d at 271 ("Preemption is an affirmative defense, and Merck has not carried its burden to prove that it is entitled to that defense as a matter of law. The *Levine* 'clear evidence' standard is demanding and fact-sensitive.").

A. Background on Plavix Approval and CAPRIE

The FDA initially approved Plavix for market in 1997, based entirely on the results of the 1996 CAPRIE study. *See* Ex. A (CAPRIE study). This study compared Plavix to aspirin for the prevention of heart attack and stroke in patients with previous heart attack or stroke or established peripheral arterial disease. *See id*. Among the most common side effects of Plavix noted in CAPRIE was bleeding. *See id.* However, it was thought based on CAPRIE that Plavix posed significantly less risk of bleeding than aspirin, the standard therapy. Notably, the aspirin arm of the CAPRIE study used a dosage of 325mg – which would be considered supra-therapeutic today. *See id*. Based partly on this presumption, risk information pertaining to bleeding was relegated to the "Precautions" section of the Plavix label. *See* Ex. I (1997 Plavix Label). However, aspirin, the comparison drug in the CAPRIE study, had information about bleeding in the "Warnings" section. *See* Ex. D (Aspirin Label). Because CAPRIE is the only study that occurred pre-approval, it is the only study that applies to Defendant's arguments.

B. CURE

The 2002 CURE study compared dual therapy with aspirin and Plavix to aspirin alone in patients with acute coronary syndrome ("ACS"). See Ex. J (CURE study). Although it was presumed that dual therapy would present a greater risk of bleeding than aspirin alone, the

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Reg. at 49,604). The court further notes that this is also the standard that governs whether FDA should accept such a warning. *Id.* (citing 21 C.F.R. § 201.57(c)(6)(i)).

bleeding observed in the dual therapy arm in CURE was higher even than expected. *See id*. This led to additional risk information being included in the Plavix label in reference to dual therapy. See Ex. K (2003 Plavix PDR). However, despite the suggestion that the greater-than-expected bleeding risk with dual therapy could have been due to the contribution of Plavix, Defendants did not further investigate the association between Plavix alone and bleeding events. Further, despite the suggestion that Plavix might do more to contribute to bleeding events than was observed in CAPRIE, Defendants chose not to pursue a CBE amendment elevating bleeding to the "Warnings" section of the label.

C. MATCH

The 2004 MATCH trial compared dual therapy with aspirin and Plavix to Plavix alone in patients with recent stroke or transient ischemic attack ("TIA"). *See* Ex. L (MATCH study). As expected, dual therapy presented a significantly higher risk of bleeding than Plavix alone; consequently, and because no significant benefit of dual therapy was observed, risk information was added to the Plavix label suggesting that dual therapy not be used in patients who fit the MATCH patient profile. *See* Ex. M (2006 Plavix PDR). However, the results of MATCH also reflected higher-than-expected bleeding rates in the Plavix arm of the trial. Indeed, based on these results, BMS scientist Mel Blumenthal remarked that, in his opinion, the Plavix label did not sufficiently warn doctors about the risks of bleeding with Plavix alone. *See* Ex. G (Blumenthal email) ("The current US Plavix labeling has nothing about bleeding in the 'Warnings' section, and the wording in the 'Precautions' section is relatively weak…"). However, despite the new information contained in the MATCH study, Defendants made no attempt to use the CBE regulation or any other process to add or strengthen the risk information pertaining to the bleeding risk of Plavix alone.

D. CHAN and CHARISMA

These studies, discussed in further detail below, provided new data sufficient to render the Plavix label inadequate in other ways, beside the placement of the bleeding risk information in the "Warnings" Section. The 2005 Chan study compared the gastrointestinal safety of Plavix alone with aspirin plus a stomach-protecting proton pump inhibitor ("PPI"). *See* Ex. C (Chan study). Even setting aside the comparator, this study produced clinically significant new data about the bleeding risk of Plavix alone. Bleeding with Plavix was, like in MATCH, higher than expected.[22] Indeed, bleeding with Plavix was so prevalent that the study's authors (who were not funded by Defendants) questioned the gastrointestinal safety of Plavix *in general*. *Id.* ("Our results raise doubt about the gastrointestinal safety of [Plavix] even in the absence of active ulcers."). This information was more than sufficient to permit Defendants to amend their label to satisfy state law under the CBE regulation. However, Defendants decided to refrain from doing so, to the detriment of doctors and patients.

The 2006 CHARISMA study compared dual therapy to aspirin alone in both patients with symptomatic atherosclerotic diseases other than ACS (similar to CAPRIE) and asymptomatic patients with several "risk factors" for heart attack and stroke. *See* Ex. N (CHARISMA study). Although, like CURE, CHARISMA did not study Plavix alone, the extremely high rate of bleeding observed in the dual therapy arm should have obliged Defendants to re-review Plavix bleeding data from CAPRIE onward and reassess whether

[22] Although patients in the Chan study had an admittedly higher risk of GI bleeding, given their previous ulcer disease, rates of recurrent bleeding in patients with *healed* ulcers in Chan was 8.6% - over four times the GI bleed rate seen in CAPRIE. *Compare* Ex. C (Chan study) (recurrent bleed rate of 8.6%) *with* Ex. A (CAPRIE study) (overall GI bleed rate of 1.99%). Similarly, patients in Chan who took Plavix experienced lower GI bleeding, which would not be affected by previous ulcer disease, at a rate of 4.6%, over twice the rate reported in CAPRIE. *See* Ex. C (Chan study) (noting lower GI bleed rate of 4.6%).

bleeding should be moved to the "Warnings" section.[23] That Defendants did not in fact do so does not negate that CHARISMA (or CURE) constitute "newly acquired information," as the Supreme Court has clarified that a drug manufacture cannot establish a preemption defense by refraining from engaging in new analyses of old data that were scientifically feasible. *See Levine*, 555 U.S. at 570.

E. Legal Effect of this Information

All of the above information was derived from study data which was received by Defendants long after FDA approval. Consequently, it is all unambiguously "newly acquired information" under the CBE standard as discussed in *Levine*. Thus, although under no obligation to do so under the burden shifting regime set up by *Levine* and F.R.C.P. 56, Plaintiffs have provided affirmative evidence that Defendants could have unilaterally changed their label to reflect the warnings Plaintiffs allege were necessary. Therefore, Defendants' preemption argument must fail, and this motion must be denied in its entirety.

F. Information from the Chan and CHARISMA Studies Provide Additional Bases for Change to the Plavix Label under CBE.

Defendants' contention that Plaintiffs do not claim any inadequacy in Plavix's label based on "newly acquired information" obtained after Plavix's initial FDA approval is further belied by their choice to ignore Plaintiffs' allegations stemming from the Chan and CHARISMA studies.

The results of both CHARISMA and the Chan study are undeniably "newly acquired information" for purposes of the CBE regulation. The Chan study was published in 2005. *See* Ex. C (Chan study). CHARISMA was published in 2006. *See* Ex. N (CHARISMA study). Neither of these studies, both coming out more than seven years after Plavix's initial approval,

[23] Almost two percent of those enrolled in the dual therapy arm of CHARISMA suffered "severe" bleeding, and about 0.3% of the enrollees randomized to dual therapy had fatal bleeds. *See* Ex. N (CHARISMA study).

were considered by FDA when it approved Plavix's initial labeling. As such, both of these studies are unambiguously "newly acquired information" for purposes of allowing Defendants to strengthen the warnings in their label under the CBE regulation. *See Levine*, 555 U.S. at 568; 21 C.F.R. § 314.70(c)(6)(iii)(A). It is therefore Defendants' burden to show clear evidence that FDA would have rejected changes to Plavix's label based on these studies under the CBE regulation – which Defendants have not even attempted to do. Consequently, Plaintiffs' claims based on these studies are clearly in no way preempted by federal law, and Defendants' argument that all of Plaintiffs' claims are preempted becomes completely untenable.

Defendants claim to be unable to figure out the gravamen of Plaintiffs' claims; perhaps that is why Plaintiffs' claims relating to Chan and CHARISMA receive no treatment whatsoever in Defendants' brief. *See Def. Brief* at 1. However, a quick read-through of the Complaints filed in this matter would reveal that Plaintiffs have alleged inadequacies in Plavix's label relating to both the Chan study and CHARISMA. Defendants' reasoning in failing to address these claims is obscure; however, their Brief suggests they only considered claims that were referenced in Plaintiffs' general expert reports. *See Def. Brief* at 1-2. However, Plaintiffs note that both Chan and CHARISMA deal with particular subsets of patients, and thus are not common to all plaintiffs.[24] Consequently, claims relating to these studies would not necessarily appear in the "general" expert reports – Plaintiffs reserve the right to serve case-specific reports relating to these claims when Plaintiffs to whom they apply are in the trial pool. This is not currently the case.

Due to the presence of cases to which the Chan and CHARISMA studies are relevant in this litigation, and due to the fact that claims arising from the non-inclusion of these studies in

[24] Chan dealt with patients with prior ulcer bleeding. *See* Ex. C (Chan study). CHARISMA dealt with patients without symptomatic atherosclerotic disease that nevertheless had several "risk factors." *See* Ex. N (CHARISMA study).

Plavix's label are clearly and unambiguously not preempted, Defendants' motion for summary judgment as to all plaintiffs is inappropriate and must fail. At the very least, on this basis alone, summary judgment is not an appropriate remedy in any case in which claims based on Chan or CHARISMA are implicated.

III. PLAINTIFFS' CLAIMS SHOULD NOT BE DISMISSED FOR FAILURE TO PROVIDE EXPERT TESTIMONY.

As a separate basis for summary judgment, Defendants claim that Plaintiffs' claims should be dismissed for failure to provide expert testimony on the subject of the adequacy of Plavix's label. At the outset, Plaintiffs note that Defendants concede that Plaintiffs have produced such evidence, in the form of the opinions of Plaintiffs' expert Dr. Randall Tackett. *See Def. Brief* at 27. It seems Defendants' argument is premised entirely on the assumption that this Court will exclude Dr. Tackett's testimony. Defendants have provided no other basis for granting summary judgment for lack of expert testimony; accordingly, if the Court does not exclude Dr. Tackett, then Defendants' motion is baseless and must be denied. However, even if Dr. Tackett were to be excluded, Defendants have not demonstrated entitlement to summary judgment on this basis, and their motion must be denied.

A. Defendants' Motion for Summary Judgment on the Basis of Expert Testimony is Untimely.

Defendants' motions to exclude are untimely, as the lack of cases in the trial pool renders judgment on expert issues premature. Consequently, Defendants' motion for summary judgment based on the motions to exclude should also be denied.

Because there are no cases in the trial pool, it would be impossible for Plaintiffs to know at this juncture what specific information will be required to prove inadequacy in the various

states whose law governs. A summary judgment motion on this basis is therefore premature. Plaintiffs' position is that the only expert testimony required at this point is testimony regarding causation, which Plaintiffs have provided in the report of Dr. Schneller, whom Defendants have not even motioned to exclude.[25] Courts have frequently denied the relief that Defendants seek, finding that the lack of expert testimony bearing on adequacy of a drug label is not grounds for granting judgment for defendants.[26] Further, Defendants have never taken the position that Plavix does not cause bleeding, nor could they. In fact, they openly agree with Plaintiffs' position that Plavix does increase the risk of bleeding in persons exposed to the drug.

Plaintiff notes that all of the cases cited by Defendant regard individual cases brought to summary judgment after extensive case-specific discovery – which can include case-specific expert reports.[27] Because adequacy is essentially a case specific issue due to the interaction of state law, and because no specific cases are currently in the trial pool, Defendants' motion is untimely and should be denied.

B. There is Expert Testimony Other than Dr. Tackett's Which Establishes the Inadequacy of Plavix's Label

Defendants claim that only Dr. Tackett has testified that the Plavix label is inadequate; however, both Plaintiffs' Expert Dr. Schneller and Defendants' Expert Dr. Feigel have given opinions that establish the inadequacy of the Plavix label. No motion to exclude either of these experts has been filed at this time. As such, even if the Court chooses to exclude Dr. Tackett's opinions, Defendants' motion for summary judgment must fail.

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[25] Notably, Defendants' own regulatory expert, whom they engaged to challenge Dr. Tackett's testimony, Dr. David Feigel, agrees that the subject of adequacy of a drug label should be posed to a jury. *See* Ex. O (Feigel Dep. at 39:24-40:3) ("My opinions are what they are, but it's up to the jury to decide as to the adequacy of the labels").

[26] *See, e.g., Rodriguez v. Depuy Orthopaedics, Inc.*, 2017 U.S. Dist. LEXIS 34139 (N.D. Tex. Jan. 3, 2017) (denying defendants' motion for JMOL despite defendants' assertion that plaintiff lacked expert testimony relating to the adequacy of a device label).

[27] *See, e.g., LaBarre v. Bristol-Myers Squibb, Co.*, 2013 WL 144054 (D.N.J. Jan. 11, 2013).

Plaintiff's causation expert, Dr. Stanley Schneller, has also offered testimony that establishes that Defendants' Plavix label was inadequate. In his report, Dr. Schneller, like Dr. Tackett, took issue with Defendants' placement of bleeding information outside of the "Warnings" section. *See* Ex. P (Schneller Report, at § 5(a)). Dr. Schneller opined that the placement of this information outside the "Warnings" section made it unlikely that doctors would read it. *See id.* This opinion is sufficient to prove that the Plavix label is inadequate. If the label is not likely to alert doctors to the risks of a drug, then that label is obviously inadequate. It would be easy for a lay juror to understand this common-sense argument, obviating the need for further expert testimony. Consequently, Dr. Schneller's opinions are sufficient to sustain Plaintiffs' case, and Defendants' motion for summary judgment must fail.

Furthermore, Defendants' own expert, Dr. Feigel, has provided testimony that is sufficient to establish the inadequacy of Defendants' label. At deposition, Dr. Feigel affirmed that FDA regulations *require* drug companies to include "serious adverse reactions and potential safety hazards, limitations in use by them, and steps that should be taken if they occur." *See* Ex. O (Feigel Dep. at 73:18-74:24). Dr. Feigel agreed that bleeding, especially the serious and potentially fatal bleeding that can be the result of Plavix exposure, would fit the criteria for appearing in the "Warnings" section under this regulation. *See id.* However, Defendants never did put bleeding information into the "Warnings" section of the label. *See id.* This testimony is *also* sufficient to help a lay juror understand the inadequacy of Plavix's label. If the placement of the bleeding information in the label is violative of FDA regulations, it is common sense that the label is inadequate. This argument is not defeated by the fact that FDA knew of this information at the time of initial approval and allowed Defendants then to proceed without placing it in the "Warnings" section, because, as established above, Defendants subsequently

received additional information from post-approval studies that obligated them to make a unilateral amendment under the CBE regulation. Consequently, Dr. Feigel's testimony is itself sufficient to establish the inadequacy of Defendants' label.

For the above reasons, even if the Court decides to exclude Dr. Tackett's testimony, there is sufficient basis in expert testimony to sustain Plaintiffs' case at summary judgment; hence, Defendants' motion must be denied.

CONCLUSION

For the foregoing reasons, this court should DENY Defendants' Omnibus Motion for Summary Judgment in its entirety.

DATED: October 30, 2017

Respectfully submitted,

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PLAVIX MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (NO. II)	MDL No. 2418
This Document Relates to: ALL CASES	**CERTIFICATION OF SHAYNA E. SACKS IN OPPOSITION TO DEFENDANTS' OMNIBUS MOTION FOR SUMMARY JUDGMENT**

SHAYNA E. SACKS, of full age and being of sound mind, hereby certifies and says:

1. I am an attorney-at-law of the State of New York and a Partner of the law firm of Napoli Shkolnik, PLLC, attorneys for Plaintiffs. As such, I am and have been personally involved in the handling of this matter, and my Certification is based upon my personal knowledge. I submit this Certification in opposition to Defendants' Omnibus Motion for Summary Judgment.
2. Attached hereto as Exhibit A is a true and correct copy of a study, published in The Lancet on November 16, 1996, entitled *A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)*, which is in the public record.
3. Attached hereto as Exhibit B is a true and correct copy of a letter sent to defendant Sanofi from an FDA Regulatory Review Officer on December 11, 1997, detailing the agency's objections to certain promotional materials pertaining to Plavix, which was obtained from the Defendants in Discovery.
4. Attached hereto as Exhibit C is a true and correct copy of a study, published in the New England Journal of Medicine in 2005, entitled *Clopidogrel versus Aspirin and*

Esomeprazole to Prevent Recurrent Ulcer Bleeding and authored by Francis K.L. Chan, *et al*., which is in the public record.

5. Attached hereto as Exhibit D is a true and correct copy of the approved labeling for aspirin, which is in the public record.
6. Attached hereto as Exhibit E is a true and correct copy of the approved labeling for Effient, which is in the public record.
7. Attached hereto as Exhibit F is a true and correct copy of the approved labeling for Brilinta, which is in the public record.
8. Attached hereto as Exhibit G is a true and correct copy of an email authored by Melvin Blumenthal, a scientist in the employ of defendant Bristol-Myers Squibb, and sent on April 13, 2004, which was obtained from the Defendants in Discovery.
9. Attached hereto as Exhibit H is a true and correct copy of the Report of Plaintiff's expert Dr. Randall Tackett, produced and obtained pursuant to this litigation.
10. Attached hereto as Exhibit I is a true and correct copy of the approved label for Plavix, revision of November 17, 1997, which is in the public record.
11. Attached hereto as Exhibit J is a true and correct copy of a study, published in New England Journal of Medicine on August 16, 2001, entitled *Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation (CURE)*, which is in the public record.
12. Attached hereto as Exhibit K is a true and correct copy of the 2003 Physician's Desk Reference ("PDR") entry for Plavix, which is in the public record.
13. Attached hereto as Exhibit L is a true and correct copy of a study, published in The Lancet on July 24, 2004, entitled *Aspirin and clopidogrel compared with clopidogrel*

alone after recent ischaemic stroke of transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial, which is in the public record.

14. Attached hereto as Exhibit M is a true and correct copy of the 2006 Physician's Desk Reference ("PDR") entry for Plavix, which is in the public record.

15. Attached hereto as Exhibit N is a true and correct copy of a study, published in the New England Journal of Medicine on April 20, 2006 and entitled *Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA)*, which is in the public record.

16. Attached hereto as Exhibit O is a true and correct copy of the transcript of the deposition of Defendants' expert Dr. David Feigel, Jr., taken on October 13, 2017 pursuant to this litigation, which was obtained from the court reporter.

17. Attached hereto as Exhibit P is a true and correct copy of the Report of Plaintiff's expert Dr. Stanley Schneller, produced and obtained pursuant to this litigation.

I certify under penalty of perjury that the foregoing is true and correct.

DATED: October 30, 2017

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PLAVIX MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (NO. II)	MDL No. 2418
This Document Relates to: ALL CASES	**PLAINTIFFS' STATEMENT IN RESPONSE TO DEFENDANTS' SEPARATE STATEMENT OF MATERIAL FACTS NOT IN DISPUTE**

Para. #	**Defendants' Statement of "Undisputed Fact"**
1.	*Plavix (clopidogrel bisulfate) is a drug that inhibits blood platelets from forming clots.* **Plaintiffs' Response** **Undisputed.**
Para. #	**Defendants' Statement of "Undisputed Fact"**
2.	*The U.S. Food and Drug Administration ("FDA") approved Plavix for use as monotherapy (*i.e., *taken without another drug, such as aspirin) in patients with recent heart attack, stroke or diagnosed peripheral arterial disease ("PAD") in November 1997.* **Plaintiffs' Response** **Undisputed**.

Para. #	**Defendants' Statement of "Undisputed Fact"**
3.	*As part of that approval process, FDA reviewed and considered the safety and efficacy of the drug, including bleeding data reported in the CAPRIE trial on which approval was based.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
4.	*As part of that initial approval process, FDA approved Plavix's label.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
5.	*The risk of bleeding has been disclosed in the Plavix label since its initial approval in 1997. This includes disclosures of bleeding risks in the "Contraindications," "Precautions," and "Adverse Reactions" sections of the label.*

Plaintiffs' Response

Disputed.

Objection: vague and ambiguous as to "the risk of bleeding" and "disclosed." Plaintiffs do not dispute that the Plavix label did reference bleeding in the sections identified by Defendants. However, Plaintiffs allege both that Defendants provided insufficient information about bleeding, and presented it in such a way as to minimize its apparent significance. *See* Ex. H (Report of Dr. Tackett, at ¶ 192). Consequently, Plaintiffs do not agree that Defendants disclosed the

information they were legally required to under relevant state law, rendering this fact disputed.

Para. # **Defendants' Statement of "Undisputed Fact"**

6. *Following submission of a supplemental NDA, FDA approved Plavix for dual therapy with aspirin for the treatment of patients with particular types of acute coronary syndrome ("ACS"), on the basis of the CURE trial.*

Plaintiffs'Plaintiffs' Response

Undisputed.

Para. # **Defendants' Statement of "Undisputed Fact"**

7. *Following submission of another supplemental NDA, FDA approved Plavix for dual therapy with aspirin for the treatment of patients with additional forms of ACS, on the basis of the CLARITY and COMMIT trials.*

Plaintiffs' Response

Undisputed

Para. # **Defendants' Statement of "Undisputed Fact"**

8. *Plaintiffs served three generic expert reports in this litigation: from Dr. Lemuel Moyé, Dr. Randall Tackett, and Dr. Stanley Schneller.*

Plaintiffs' Response

Undisputed.

Para. # **Defendants' Statement of "Undisputed Fact"**

9. *Dr. Stanley Schneller did not address the adequacy of Plavix's labeling in his expert report, nor did he give the opinion that Plavix's risks outweigh its benefits.*

Plaintiff's Response

Disputed.

Dr. Schneller opined in his report that risk information about bleeding in patients who took Plavix was placed by Defendants in a section of the label that doctors were unlikely to review. *See* Ex. P (Report of Dr. Schneller, at § 5(a)). A reasonable jury could conclude that a warning placed in a section unlikely to be read by doctors is not adequate to warn doctors about the risks of the drug. Therefore, Dr. Schneller provides expert testimony, as a practicing physician, that directly bears on the adequacy of Plavix's drug label.

Para. #	**Defendants' Statement of "Undisputed Fact"**
10.	*Dr. Lemuel Moyé did not address the adequacy of Plavix's labeling in his expert report.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
11.	*Dr. Randall Tackett did not give the opinion that Plavix's risks outweigh its benefits in his expert report.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
12.	*The "main thrust" of Dr. Tackett's opinions is that the placement of bleeding risk information in Plavix labeling was inadequate.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
13.	*Dr. Tackett offered the opinion that Plavix's label was inadequate because serious bleeding risk information should have appeared in the "Warnings" section of the Plavix labeling or in a "Black Box" warning.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
14.	*Dr. Tackett's opinion about the asserted inadequacy of the Plavix labeling is based on the placement of bleeding risk information in the original Plavix labeling*.

Plaintiffs' Response

Disputed.

Objection: misstates the evidence. At all relevant times, the "Warnings" section of the Plavix label contained no information about bleeding. *See*, *e.g.* Ex. M (2006 Plavix PDR). Therefore, although the original Plavix label also exhibited this inadequacy, Dr. Tackett's opinion is relevant to the adequacy of Plavix's label beyond the initial approval in 1997. As Defendants gained more information about Plavix, FDA regulations required them to amend the Plavix label to elevate bleeding to a "Warning." Dr. Tackett's report ultimately bears on this.

Para. #	Defendants' Statement of "Undisputed Fact"
15.	*FDA understood the bleeding risk associated with Plavix before FDA approved the content and placement of the bleeding information in the original Plavix labeling.*

Plaintiffs' Response

Disputed.

Objection: vague and ambiguous as to "the bleeding risk associated with Plavix." The FDA did not, for example, understand that Plavix was much more likely to cause ulcer bleeding than a regimen of aspirin plus PPI when they initially approved Plavix, because the Chan study had not yet been performed. The information about the bleeding risks of Plavix considered by FDA, even if sufficient to justify approval in 1997, was far less comprehensive than what is available today. After receiving this information, Defendants, not FDA, bore the responsibility to amend the Plavix label.

Para. #	Defendants' Statement of "Undisputed Fact"
16.	*Dr. Tackett has not offered an opinion that FDA was unaware of any pertinent bleeding information when it approved the original Plavix labeling or that new bleeding risk information obligated Defendants to revise the label through a "Changes Being Effected" labeling revision.*

Plaintiffs' Response

Disputed.

Objection: misstates the evidence. Dr. Tackett discusses the various post-approval studies that came out *after* FDA approved the original Plavix label, and

the information about bleeding that Defendants obtained from those studies. *See* Ex. H (Report of Dr. Tackett, at ¶¶ 102-06). Dr. Tackett also opines that the Plavix label was inadequate, on the basis of not including this information. *See id* at ¶¶ 191-92. Although Dr. Tackett does not specifically reference the "Changes Being Effected" ("CBE") regulation, his testimony establishes that Defendants could have made use of it. The "newly acquired information" standard, as required by the CBE regulation is non-technical, and easily understood by a lay juror. Based on this standard, Dr. Tackett's testimony establishes both that Defendants had "newly acquired information" and that their label was inadequate without it. Consequently, Dr. Tackett *does* provide an opinion on this matter.

Para. # **Defendants' Statement of "Undisputed Fact"**

17. *Defendants were required to obtain prior approval from FDA for the original Plavix labeling.*

Plaintiffs' Response

Undisputed.

Para. # **Defendants' Statement of "Undisputed Fact"**

18. *FDA must pre-approve "Black Box Warnings."*

Plaintiffs' Response

Undisputed.

Para. # **Defendants' Statement of "Undisputed Fact"**

19. *Dr. Moyé offered the opinion that FDA should not have approved Plavix for any of its approved indications.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
20.	*Dr. Moyé testified that he raised his concerns regarding the CAPRIE trial and Plavix's initial approval with FDA, and that his opinions were based on published data and clinical trials available to FDA at the time of its approval for each indication.*

Plaintiffs' Response

Undisputed.

Para. #	**Defendants' Statement of "Undisputed Fact"**
21.	*Plaintiffs have disclosed no expert opinion that Plavix's labeling is inadequate, except for Dr. Tackett's opinion.*

Plaintiffs' Response

Disputed.

As stated above, Dr. Schneller's opinion also bears on the adequacy of the Plavix label, in that, in his expert opinion, risk information about Plavix was placed in a section of the label that was unlikely to be read by doctors. *See* Ex. P (Report of Dr. Schneller, at § 5(a)). By common sense, any warning that is placed such that it will not be read is inadequate. The testimony of a physician that physicians are unlikely to read a warning is sufficient to help the jury understand whether a label adequately warns physicians. As such, Dr. Schneller has opined on the adequacy of the Plavix label.

Additionally, Defendants' own expert, Dr. Feigel, testified as to issues that bear on the inadequacy of Defendants' label. Dr. Feigel testified that he believed that bleeding as it pertains to Plavix fits the criteria for information that FDA regulations *require* drug companies to put in the "Warnings" section of the approved labeling. *See* Ex. O (Dep. of Dr. Feigel, at 73:18-74:17). However, as Dr. Feigel testified, Defendants never added bleeding to the "Warnings" section of the label. *See id.* at 74:18-24. This testimony also establishes the inadequacy of Plavix's label. The fact that Plavix's label fell short of the standards set by the FDA is evidence upon which a reasonable jury could conclude that the label was inadequate. The fact that the FDA did not determine that bleeding needed to be in the "Warnings" section is immaterial. As stated in Plaintiffs' Opposition Brief, Defendants received ample information *post-approval* that *obligated* them to reopen the matter with FDA pursuant to the "Changes Being Effected" regulation. Since Defendants chose never to do so, there is no evidence that the FDA did not consider the Plavix labeling inadequate at later times. As such, Dr. Feigel's testimony is itself sufficient to establish that Plavix's label is inadequate as a matter of law.

Para. #	**Defendants' Statement of "Undisputed Fact"**
22.	*Plaintiffs have disclosed no expert opinion that Plavix's risks outweigh its benefits, except for Dr. Moyé's opinion.*

Plaintiffs' Response

Undisputed.

Dated: October 30, 2017

/s/ Shayna E. Sacks

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PLAVIX MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (NO. II)	MDL No. 2418
This Document Relates to: ALL CASES	**[PROPOSED] FORM OF ORDER**

Before the Court is an Omnibus Motion for Summary Judgment, filed on behalf of Defendants Bristol-Myers Squibb Co., Sanofi-Aventis U.S. LLC, Sanofi-Aventis U.S. Inc., and Sanofi-Synthelabo Inc. Upon consideration of all papers submitted, including moving, opposition, and reply papers, and of oral argument as requested by the parties, and for good cause shown:

IT IS, on this _____ day of _____, 2017,

HEREBY ORDERED that summary judgment in favor of Defendants is **DENIED** as to all counts; and it is further

ORDERED that a copy of this Order be served on all counsel of record within _____ days hereof.

_____
HON. FREDA L. WOLFSON, U.S.D.J.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PLAVIX MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (NO. II)	MDL No. 2418
This Document Relates to: ALL CASES	**CERTIFICATE OF SERVICE**

I, SHAYNA E. SACKS, hereby certify that I caused the a true and correct copy of the foregoing to be electronically filed with the Clerk of the Court using the CM/ECF system, which will send notification of such filing to the e-mail addresses denoted on the Electronic Mail Notice List.

I certify under penalty of perjury that the foregoing is true and correct.

Dated: October 30, 2017

/s/ Shayna E. Sacks

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