UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	)	**MDL No. 16-2740**
	)	**SECTION: "H" (5)**
This document relates to:	)	
Hilda Adams, 16-17583	)	
Gloria Cooper, 18-194	)	
Carol Woodson, 17-12674	)	
Arquice Conley, 18-9799	)	
Tina Hickey, 18-4731	)	

ORDER AND REASONS

Before the Court are Defendant Accord Healthcare Inc.'s Motion for Summary Judgment on Preemption Grounds (Doc. 13425), Defendant Sandoz Inc.'s Motion for Summary Judgment on Preemption Grounds (Doc. 13445), and Defendant Hospira's Motion for Summary Judgment Based on Preemption (Doc. 13857). The Court held oral argument on Accord and Sandoz's Motions on February 17, 2022, and on Hospira's Motion on April 14, 2022. For the following reasons, the Motions are **DENIED**.

BACKGROUND

Plaintiffs in this multidistrict litigation ("MDL") are suing several pharmaceutical companies that manufactured and/or distributed a chemotherapy drug, Taxotere or docetaxel,[1] that Plaintiffs were administered for the treatment of breast cancer or other forms of cancer. Among these companies are defendants sanofi-aventis U.S. LLC and Sanofi U.S. Services

[1] Docetaxel is the generic version of Taxotere, although the Court uses the term "generic" loosely.

Inc. (collectively, "Sanofi") as well as Accord Healthcare, Inc. ("Accord"); Sandoz Inc. ("Sandoz"); Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc.; and Hospira, Inc. (collectively, "Hospira"). Plaintiffs allege that the drug caused permanent alopecia—in other words, permanent hair loss—also referred to as "permanent chemotherapy-induced alopecia" ("PCIA"). Plaintiffs bring claims of failure to warn, negligent misrepresentation, fraudulent misrepresentation, and more.

The three Motions before the Court were filed by Accord, Sandoz, and Hospira. Accord's Motion identifies three plaintiffs—Hilda Adams, Carol Woodson, and Gloria Cooper—each of whom received Accord's docetaxel as part of her chemotherapy regimen. Plaintiff Adams was treated from January 4, 2013 to April 24, 2013. Plaintiff Woodson was treated from May 1, 2013 to July 3, 2013. And Plaintiff Cooper was treated from November 17, 2014 to March 23, 2015.

Sandoz's Motion identifies Plaintiff Arquice Conley. Plaintiff Conley was treated with Sandoz's docetaxel as part of her chemotherapy regimen from October 14, 2011 to January 24, 2012. Lastly, Hospira's Motion identifies Plaintiff Tina Hickey. Plaintiff Hickey was treated with Hospira's docetaxel as part of her chemotherapy regimen from October 25, 2013 to February 6, 2014.

Accord, Sandoz, and Hospira (collectively, "Defendants") each move this Court to grant summary judgment in their favor, arguing that Plaintiffs' state-law failure-to-warn claims are preempted by federal law. Specifically, Defendants contend that at the time of Plaintiffs' chemotherapy treatments, federal law precluded Defendants from unilaterally revising their docetaxel labels to include the warning that Plaintiffs claim state law required. Plaintiffs oppose.

LAW AND ANALYSIS

The doctrine of preemption derives from the U.S. Constitution's Supremacy Clause, which provides 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."[2] "Where state and federal law 'directly conflict,' state law must give way."[3] Such a conflict exists "where it is 'impossible for a private party to comply with both state and federal requirements.'"[4] In the context of state-law claims concerning the adequacy of drug labeling, the Supreme Court has instructed that "the question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."[5] The answer to that question comes from the federal laws and regulations governing drug approval and labeling. Thus, before addressing the parties' arguments, this Court provides a broad overview of the federal regulation of prescription drugs as well as the regulatory history of Sanofi's Taxotere and each Defendant's docetaxel.

I. Federal Regulation of Prescription Drugs

A. Approval Pathways

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), drug manufacturers must receive approval from the United States Food and Drug Administration ("FDA") before introducing any drug into interstate commerce.[6] "Originally, the same rules applied to all drugs. In 1984, however, Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly called the Hatch-Waxman Amendments," which established two

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[2] U.S. CONST. art. VI, cl. 2.
[3] PLIVA, Inc. v. Mensing, 564 U.S. 604, 617 (2011) (quoting Wyeth v. Levine, 555 U.S. 555, 583 (2009)).
[4] *Id.* (quoting Freightliner Corp. v. Myrick, 514 U.S. 280, 287 (1995)).
[5] *Id.* at 620 (citing *Wyeth*, 555 U.S. at 573).
[6] 21 U.S.C. § 355(a).

types of drug applications.[7] The first type is known as "new drug applications," or NDAs, the requirements of which are set forth in § 505(b) and (c) of the FDCA.[8] The second type is known as "abbreviated new drug applications," or ANDAs, the requirements of which are set forth in § 505(j) of the FDCA.[9] Generally speaking, there are three pathways to approval, two involving NDAs and the other involving ANDAs.

The traditional pathway, set forth in § 505(b)(1), requires a manufacturer seeking approval of a new drug to submit an NDA. Among other requirements, the NDA must include full reports of investigations of safety and effectiveness and must show that the proposed label is accurate and adequate.[10] "Meeting those requirements involves costly and lengthy clinical testing."[11]

Under § 505(j), however, a manufacturer may submit an ANDA if it is seeking approval of a drug that is the same in all relevant respects as a previously approved drug, otherwise known as the "reference listed drug" ("RLD"). A § 505(j) ANDA applicant must demonstrate that its drug has the same active ingredients as the RLD, that "the route of administration, the dosage form, and the strength of the new drug are the same" as the RLD, and that its product is "bioequivalent" to the RLD.[12] Because of these similarities, the ANDA process permits the manufacturer to incorporate the safety and efficacy data submitted in the NDA of the RLD, eliminating the need for the ANDA applicant to conduct duplicate clinical trials already performed on the

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[7] *Mensing*, 564 U.S. at 612.
[8] *See* 21 U.S.C. § 355(b), (c). Sections 505(b) and (c) of the FDCA are codified at 21 U.S.C. § 355(b) and (c).
[9] *See* 21 U.S.C. § 355(j). Section 505(j) of the FDCA is codified at 21 U.S.C. § 355(j).
[10] *Mensing*, 564 U.S. at 612 (first citing 21 U.S.C. § 355(b)(1), (d); and then citing *Wyeth,* 555 U.S. at 567).
[11] *Id.* (first citing 21 U.S.C. § 355(b)(1), (d); and then citing D. Beers, Generic and Innovator Drugs: A Guide to FDA Approval Requirements § 2.02[A] (7th ed. 2008)).
[12] *Id.* at 628 (Sotomayor, J., dissenting) (citing 21 U.S.C. § 355(j)(2)(A)(ii), (iii), (iv)).

RLD.[13] Additionally, a § 505(j) ANDA applicant must "show that the [safety and efficacy] labeling proposed" in the ANDA "is the same as the labeling approved for the [RLD]."[14]

The final pathway, set forth in § 505(b)(2), is available to a manufacturer of a drug "that ha[s] changes from a [listed] drug, such that an ANDA application is unavailable, but whose changes are so slight that a manufacturer may rightly rely on the 'full reports of investigations' of the [listed] drug to establish the new drug's safety and efficacy."[15] Pursuant to § 505(b)(2), these manufacturers may file an NDA "even though those investigations 'were not conducted by or for the applicant and . . . the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.'"[16] "The § 505(b)(2) NDA applicant must submit additional data to the FDA that demonstrates that any differences between the original drug and the § 505(b)(2) drug will not affect the § 505(b)(2) drug's safety and efficacy."[17] "But, having done that, a § 505(b)(2) applicant can avoid preclinical and certain human studies necessary in full NDA applications."[18] Notably, unlike drugs approved via § 505(j), there is no codified statutory or regulatory requirement that § 505(b)(2) drugs contain the same label as the RLD.[19]

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[13] *Id.* at 612.
[14] *Id.* at 612–13.
[15] Ethypharm S.A. France v. Abbott Lab'ys, 707 F.3d 223, 227 (3d Cir. 2013) (quoting 21 U.S.C. § 355(b)(1)).
[16] *Id.* (quoting 21 U.S.C. § 355(b)(2)).
[17] *Id.*
[18] *Id.* (citing 21 C.F.R. § 314.54(a)).
[19] *See* 21 U.S.C. § 355(j)(2)(A)(v) (explaining that "[a]n abbreviated application for a new drug shall contain . . . information to show that the labeling proposed for the new drug is the same as the labeling approved for the [reference] listed drug"); *cf.* 21 U.S.C. § 355(b)(2) (containing no such provision).

B. Labeling Requirements

"FDA regulations set out requirements for the content, the format, and the order of the safety information on the drug label."[20]

> Those regulations require drug labels to include, among other things: (1) prominent "boxed" warnings about risks that may lead to death or serious injury; (2) contraindications describing any situation in which the drug should not be used because the risk of use outweighs any therapeutic benefit; (3) warnings and precautions about other potential safety hazards; and (4) any adverse reactions for which there is some basis to believe a causal relationship exists between the drug and the occurrence of the adverse event.[21]

"The hierarchy of label information is designed to 'prevent overwarning' so that less important information does not 'overshadow' more important information."[22] "It is also designed to exclude '[e]xaggeration of risk, or inclusion of speculative or hypothetical risks,' that 'could discourage appropriate use of a beneficial drug.'"[23]

C. Changes to Approved Labeling

The FDA's initial approval of an NDA or ANDA includes approval of the exact text that will be included in the drug's label.[24] "But FDA regulations also acknowledge that information about drug safety may change over time, and that new information may require changes to the drug label."[25] Generally, "a manufacturer may only change a drug label after the FDA approves a supplemental application."[26] Under the "changes being effected" ("CBE") regulation, however, a manufacturer may make certain changes to its label

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[20] Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1673 (2019).
[21] *Id.* (citing 21 C.F.R. § 201.57(c)).
[22] *Id. (*citing 73 Fed. Reg. 49605–49606 (2008)).
[23] *Id.* (citing 73 Fed. Reg. 2851 (2008)).
[24] *See* 21 U.S.C. § 355(d), (j)(4)(H).
[25] *Albrecht*, 139 S. Ct. at 1673 (citing 21 C.F.R. §§ 314.80(c), 314.81(b)(2)(i)).
[26] *Wyeth*, 555 U.S. at 568.

without prior FDA approval.[27] To make a CBE change, "the manufacturer must satisfy at least two requirements."[28]

> First, the change must "reflect newly acquired information." Second, the change must be for the purpose of accomplishing at least one of the five following objectives:
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> > (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling . . .;
> >
> > (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
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> > (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
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> > (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
> >
> > (E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.[29]

"The manufacturer may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval."[30]

Because holders of ANDAs "have an ongoing federal duty of 'sameness'"—meaning that the FDA's regulations require that the warning labels of drugs approved pursuant to § 505(j) must always be the same as that of the RLD—the CBE regulation is only available to ANDA holders when the change is made to "match an updated [RLD] label or to follow the FDA's instructions."[31] Relevant here, the same has not been said for § 505(b)(2) NDA

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[27] *See id.*
[28] In re Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 37 (1st Cir. 2015).
[29] *Id.* (internal citations omitted) (quoting 21 C.F.R. § 314.70(c)(6)(iii)).
[30] *Wyeth*, 555 U.S. at 568 (citing 21 C.F.R. § 314.70(c)(6)(iii)).
[31] *Mensing*, 564 U.S. at 604.

holders, despite the fact that a listed drug is also the basis for a § 505(b)(2) NDA's approval.[32]

II. The Regulatory History of Taxotere and Docetaxel[33]

Accord, Sandoz, and Hospira are all manufacturers of docetaxel, an unbranded version of Taxotere. Taxotere was developed by Sanofi and approved by the FDA in 1996 for the treatment of advanced or metastatic breast cancer. With Sanofi's patent for Taxotere set to expire in 2010, Defendants each submitted NDAs for their docetaxel products pursuant to § 505(b)(2) of the FDCA.

The original Taxotere was provided as a concentrated solution with diluent in two presentations, each with a nominal concentration of 40mg/mL per vial, and required a two-step dilution process before administration. In June 2010, the FDA approved a supplemental application submitted by Sanofi, permitting Sanofi to provide its Taxotere product as a concentrated solution with one dilution step in three presentations, all with nominal concentrations of 20 mg/mL per vial.

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[32] *See* Doc. 13595-3 at 19 (Woodcock Letter); Doc. 13596-3 at 19 (same); Doc. 13978-3 at 19 (same). This exhibit, submitted by Plaintiffs, is the FDA's consolidated response to certain citizen petitions regarding the FDA's interpretation of § 505(b)(2) of the FDCA. The letter was written by Janet Woodcock, M.D., Director for the Center for Drug Evaluation and Research, in 2003. In the letter, she explains: "[T]here are no analogues in section 505(b)(2) to the provisions in section 505(j) requiring that the product under the 505(j) application be bioequivalent to, have the same conditions of use as, and use the same labeling as the listed drug referenced. These differences do not suggest that 505(b)(2) applications cannot rely, in part, on FDA's conclusion that a listed drug is safe and effective. Rather, they support FDA's longstanding interpretation that products under 505(b)(2) applications, unlike those under ANDAs, need not be duplicates of the listed drugs referenced. If 505(b)(2) applications were limited to literature-based duplicates, surely Congress would have required that, like those approved in ANDAs, products approved in 505(b)(2) applications be bioequivalent to, have the same conditions of use as, and the same labeling as the listed drugs referenced. No such sameness requirement was included, however, because section 505(b)(2) was never intended to be limited to literature-based duplicates."

[33] The Court discussed the history of Taxotere and its label more specifically in the Order and Reasons on Sanofi's Motion for Summary Judgment Based on Preemption. *See* Doc. 11682.

Hospira submitted its § 505(b)(2) NDA in July 2007.[34] Hospira's docetaxel contained the same active ingredient, route of administration, and proposed indications as Taxotere. Hospira's docetaxel was presented in vials with a nominal concentration of 10 mg/mL per vial with one dilution step.[35] Because of the similarities between Taxotere and Hospira's docetaxel, Hospira did not submit new clinical data as part of its NDA, and the FDA relied entirely on its prior review of the Sanofi NDA for Taxotere to support the safety and efficacy of Hospira's docetaxel.[36] The FDA approved Hospira's NDA on March 9, 2011.[37]

Accord submitted its § 505(b)(2) NDA in December 2009.[38] Accord's docetaxel contained the same active ingredient, route of administration, dosage form, strength, proposed indications, and dosing regimen as Taxotere.[39] Accord's docetaxel differed from the original Taxotere only by the inclusion of two inactive ingredients: citric acid and polyethylene glycol.[40] Like Hospira, the FDA did not require Accord to submit additional studies to support the safety and efficacy of its docetaxel and relied entirely on its prior review of the Sanofi NDA for Taxotere to support the safety and efficacy of Accord's docetaxel.[41] The FDA approved Accord's NDA on June 8, 2011.[42]

Sandoz submitted its § 505(b)(2) NDA for docetaxel in September 2010.[43] Like Hospira, Sandoz's docetaxel was presented in vials with a nominal concentration of 10 mg/mL per vial and one dilution step.[44] Sandoz likewise

[34] Doc. 13857-10.
[35] Docs. 13857-11, 13857-12.
[36] Docs. 13857-11, 13857-12.
[37] Docs. 13857-11, 13857-12.
[38] Doc. 13425-10.
[39] Doc. 13425-11.
[40] *Id.*
[41] *Id.*
[42] *Id.*
[43] Doc. 13445-4 at 342.
[44] *Id.*

did not submit additional studies to support the safety and efficacy of its docetaxel, and the FDA relied on the clinical safety profile and efficacy of Taxotere to support the safety and efficacy of Sandoz's docetaxel.[45] The FDA approved Sandoz's NDA on June 29, 2011.[46]

The warnings, precautions, and adverse reactions information in the FDA-approved labeling for Defendants' docetaxel products were identical to the information in the Taxotere labeling at that time. Accordingly, Defendants included an unqualified warning about alopecia in the Adverse Reactions section of their labels.[47] Like the Taxotere labeling, Defendants' labels also included the following instruction in the Patient Counseling Information section: "Explain to patients that side effects such as . . . hair loss are associated with docetaxel administration."[48] The Patient Package Insert for each product also referenced "hair loss" as a common side effect.[49] Defendants' labeling with respect to alopecia remained unchanged from the time of approval in 2011 until after Sanofi amended its label to reflect reports of permanent alopecia associated with Taxotere in November 2015.

On November 24, 2015, Sanofi initiated a CBE change to amend the Adverse Reactions and Patient Counseling Information sections of the Taxotere labeling and the Patient Package Insert. Sanofi added the following sentence to the Adverse Reactions section: "Cases of permanent alopecia have been reported." The Patient Counseling Information section was revised to instruct doctors to "[e]xplain to patients that side effects, such as . . . hair loss (cases of permanent alopecia have been reported) are associated." Sanofi also revised the Patient Package Insert to include the following phrasing under a

[45] *Id.* at 354.
[46] *Id.*
[47] Doc. 13857-11 at 14 (Hospira); Doc. 13425-11 at 40 (Accord); Doc. 13445-4 at 239 (Sandoz).
[48] Doc. 13857-12 at 14 (Hospira); Doc. 13425-11 at 82 (Accord); Doc. 13445-4 at 279–80 (Sandoz).
[49] Doc. 13857-12 at 16 (Hospira); Doc. 13425-11 at 85 (Accord); Doc. 13445-4 at 282 (Sandoz).

section listing the most common side effects of Taxotere: "hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed." The FDA approved these changes on December 11, 2015.

On December 30, 2015, Accord submitted a CBE to update its label to reflect the changes made to the Taxotere label regarding permanent alopecia, and the FDA approved Accord's changes on July 26, 2016.[50] Sandoz submitted a CBE to do the same on March 7, 2016, and the FDA approved the changes on November 2, 2016.[51] Hospira made similar changes to its label via a CBE on March 31, 2017, which the FDA approved on September 27, 2017.[52]

III. Parties' Arguments

Plaintiffs argue that after the FDA approved Defendants' docetaxel labels but before Plaintiffs were treated with docetaxel, Defendants should have updated their docetaxel labels to include a warning about the risk of permanent alopecia and that Defendants' failure to do so violated their state-law duty to provide an adequate warning.[53] The theory of Defendants' preemption defense, therefore, is as follows. Under federal law, the only way Defendants could have independently changed their docetaxel labels was through the CBE process, which is only available if the change is based on "newly acquired information" that provides evidence of a causal association between the drug and the risk. Plaintiffs' state-law claims are, therefore, preempted because Plaintiffs cannot identify "newly acquired information" that would have permitted Defendants to independently change their labels via the CBE process before Plaintiffs were treated with docetaxel.

[50] Docs. 13425-21, 13425-22.
[51] Doc. 13445-5 at 21–22, 24–25.
[52] Doc. 13857-27.
[53] For purposes of the instant Motions only, this Court assumes that the state law applicable to each Plaintiff's claim required Defendants to include a warning in its docetaxel label about the risk of permanent alopecia.

In response, Plaintiffs emphasize that preemption is an affirmative defense that Defendants must plead and prove and, therefore, Defendants' position should be rejected because it improperly shifts the burden to Plaintiffs to disprove preemption. They argue that to prove preemption, Defendants must present "clear evidence" that the FDA would not have approved the change to their docetaxel labels, which requires that each Defendant show (1) that it "fully informed the FDA of the justifications for the warning required by state law" and (2) "that the FDA, in turn, informed the drug manufacturer, that the FDA would not approve changing the drug's label to include that warning."[54] And because Defendants cannot make this showing, they are not entitled to summary judgment, according to Plaintiffs.

This Court's analysis, therefore, proceeds in two main parts. First, the Court will determine the applicable burden of proof and who bears it. Next, the Court will determine whether that burden of proof has been satisfied.

IV. The Burden of Proof

Upon review of the applicable Supreme Court cases, this Court finds that there are two ways a defendant can prove impossibility preemption when a plaintiff challenges a label that was previously approved by the FDA: (1) if the CBE regulation was not available to it, or (2) by presenting "clear evidence" that the FDA would not have approved the warning that state law requires.[55] Neither *Wyeth*, *Mensing*, nor *Albrecht* supports Plaintiffs' contention that Defendants can only prove preemption by presenting clear evidence that the FDA would not have approved a change to their docetaxel labels.

In *Wyeth*, the Supreme Court first considered whether the unavailability of the CBE regulation preempted a plaintiff's state-law claim.[56] There, the drug

[54] *Albrecht*, 139 S. Ct. at 1672.
[55] *See Wyeth*, 555 U.S. 555; *Mensing*, 564 U.S. 604; *Albrecht*, 139 S. Ct. 1668.
[56] 555 U.S. at 568–70.

manufacturer argued, in relevant part, that the CBE regulation was not available to it because it lacked newly acquired information.[57] Notably, the Court did not say it was irrelevant whether the CBE regulation is available. Rather, the Court examined the record for newly acquired information and then found that the manufacturer could have used the CBE regulation to unilaterally change its label.[58] The Court went on to explain that "of course, the FDA retains authority to reject labeling changes made pursuant to the CBE regulation . . . [b]ut absent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for [the drug manufacturer] to comply with both federal and state requirements."[59]

In *Mensing*, the Supreme Court emphasized that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."[60] After determining that ANDA holders cannot use the CBE regulation to independently change their drug labels due to their federal duty of sameness, the Court considered and rejected the plaintiffs' separate argument that the ANDA holder could have worked with the FDA to have the RLD label changed.[61] The Court specifically held that "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes."[62]

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[57] *Id.* at 568.
[58] *Id.* at 569–70.
[59] *Id.* at 571.
[60] 564 U.S. at 620 (citing *Wyeth*, 555 U.S. at 573).
[61] *Id.* at 620–21.
[62] *Id.* at 623–24.

Most recently, in *Albrecht*, the Supreme Court granted certiorari to clarify the "clear evidence" standard it established in *Wyeth*.[63] The Court held that

> "clear evidence" is evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning.[64]

Importantly, the manufacturer in *Albrecht* "conceded that the FDA's CBE regulation would have permitted it to try to change the label"; the manufacturer was only arguing "that the FDA would have rejected that attempt."[65]

Therefore, where, as here, Defendants argue that Plaintiffs' claims are preempted because Defendants could not have used the CBE regulation to update their labels to add the warning state law required, this Court need not first consider whether the "clear evidence" standard is met; that question is secondary.[66]

As previously discussed, a CBE change must be based on newly acquired information.[67] And if the change is made "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction," there must also be "evidence of a causal association" that "satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)."[68] The parties disagree, though, over

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[63] *Albrecht*, 139 S. Ct. at 1676 ("In light of differences and uncertainties among the courts of appeals and state supreme courts in respect to the application of *Wyeth*, we granted certiorari.").
[64] *Id.* at 1672. The Court also determined that this question of agency disapproval is a question of law for a judge to decide, not a jury. *Id.* at 1679.
[65] *Id.* at 1675.
[66] *See Wyeth*, 555 U.S. at 568–73 (considering first whether the manufacturer could have used the CBE regulation, and only after finding that it could, considering whether the manufacturer had shown "clear evidence" that the FDA would have rejected the label change).
[67] 21 C.F.R. § 314.70(c)(6)(iii).
[68] *Id.* § 314.70(c)(6)(iii)(A).

who bears the burden of proving Defendants could or could not have used the CBE regulation to change their labels.

Defendants argue that it is Plaintiffs' burden to identify the information that qualifies as "newly acquired information" and that shows evidence of a causal association between docetaxel and permanent hair loss that would have permitted Defendants to change their labels via the CBE regulation. Conversely, Plaintiffs argue that preemption is an affirmative defense that a defendant must plead and prove and, therefore, Defendants' approach misapprehends the burden of proving preemption.

Indeed, the Fifth Circuit has recognized that federal preemption is an affirmative defense that a defendant must plead and prove.[69] Furthermore, the Supreme Court's *Wyeth* and *Albrecht* opinions each contain language indicating that the defendant bears the burden of proving a label change was impossible. In particular, the *Wyeth* Court found that "*Wyeth ha[d] failed to demonstrate* that it was impossible for it to comply with both federal and state requirements."[70] In *Albrecht*, the Court stated,

> The underlying question for this type of impossibility pre-emption defense is whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law. And, of course, in order to succeed with that defense *the manufacturer must show that the answer to this question is yes*.[71]

Some lower courts, however, have implemented a burden-shifting approach that requires the plaintiff to first prove that there was "newly acquired information" such that the defendant-manufacturer could unilaterally change its label pursuant to the CBE regulation; and only if the

[69] Fisher v. Halliburton, 667 F.3d 602, 609 (5th Cir. 2012) (citing Met. Life Ins. Co. v. Taylor, 481 U.S. 58, 63 (1987)).
[70] 555 U.S. at 572–73 (emphasis added).
[71] 139 S. Ct. at 1678 (emphasis added).

plaintiff satisfies that burden does it then shift to the manufacturer to show by "clear evidence" that the FDA would not have approved the labeling change.[72]

The Fifth Circuit has not opined on the applicability of this burden-shifting approach, and this Court is not inclined to abandon the general rule that a defendant bears the burden of proving its affirmative defense. Nevertheless, allocating the burden entirely to Defendants would require them to prove a negative (i.e., that there was no new information after their docetaxel was approved that would have justified a label change via the CBE regulation).[73] This Court, therefore, adopts the approach recommended in *Silverstein v. Boehringer Ingelheim Pharmaceuticals, Inc.*, in which the manufacturer bears "the ultimate burden of persuasion," but the plaintiff "bears an initial burden of production."[74]

Accordingly, when the issue for determination is whether a manufacturer could have unilaterally updated its label pursuant to the CBE regulation, Plaintiffs bear the initial burden of identifying the specific information that they contend the manufacturer could have used to modify the

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[72] *See, e.g.*, Gibbons v. Bristol-Myers Squibb Co., 919 F.3d 699, 708 (2d Cir. 2019); Utts v. Bristol-Myers Squibb Co., 251 F. Supp. 3d 644, 661 (S.D.N.Y. 2017); Ridings v. Maurice, 444 F. Supp. 3d 973, 991 (W.D. Mo. 2020); In re Incretin-Based Therapies Prods. Liab. Litig., 524 F. Supp. 3d 1007, 1018 (S.D. Cal. 2021).

[73] *See* Doc. 13477-2 at 15 (citing Silverstein v. Boehringer Ingelheim Pharm., Inc., No. 19-81188, 2020 WL 6110909, at *12 (S.D. Fla. Oct. 7, 2020)) ("Allocating the burden in the manner Plaintiff proposes imposes on the manufacturer the burden to 'prove a negative – that it acquired no new information after [the drug] was approved that would have justified a CBE modification.'"); Doc. 13857-1 at 11 (citing *Silverstein*, 2020 WL 6110909, at *12) ("[I]t is only fair to place this burden of identifying the 'newly acquired information' on the plaintiff, because the defendant cannot guess what facts the plaintiff may contend constitutes [sic] such information and cannot prove a negative.").

[74] 2020 WL 6110909, at *12. Also, this Court tailors the approach in *Silverstein* so that it applies to the availability of the CBE regulation as a whole, not just the newly acquired information requirement. The approach recommended in *Silverstein* assumes that the only requirement for a CBE change is that it be based on newly acquired information. But, as previously discussed, certain changes to the label, like adding a warning, require more than newly acquired information—there must also be evidence of a causal association that satisfies the standard for inclusion under 21 C.F.R § 201.57(c). *See* 21 C.F.R. § 314.70(c)(6)(iii)(A).

drug's label. Once Plaintiffs point to this specific information, the manufacturer bears the burden of proving that it does not meet the requirements of the CBE regulation. This approach "avoids making the manufacturers prove a negative" while remaining "faithful to the general rule that a defendant bears the ultimate burden of proving an affirmative defense."[75]

V. Impossibility Preemption Analysis

Plaintiffs, through their proposed regulatory expert, Dr. Ross, identify certain pieces of information that each Defendant had or should have had that Defendants could have used to change their labels. Defendants insist that Plaintiffs have not carried their burden because Dr. Ross does not specifically state that any of this information was "newly acquired information" or analyze why it would qualify as newly acquired information. This Court disagrees. Preemption is an affirmative defense that a defendant must plead and prove.[76] Plaintiffs have carried their burden in identifying the information they contend Defendants could have used to change their labels; Defendants are not forced to prove a negative. Rather, Defendants must show that the information identified by Plaintiffs would not have permitted them to change their labels via the CBE regulation.

A. What Can Constitute Newly Acquired Information

Defendants first argue, and this Court agrees, that the information that came available after Plaintiffs were treated with docetaxel is irrelevant. Indeed, if the information could not have been used to change the label in time to prevent a plaintiff's injuries, it is irrelevant to the failure-to-warn claim.[77]

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[75] *Silverstein*, 2020 WL 6110909, at *12.
[76] *Fisher*, 667 F.3d at 609.
[77] *See* Mahnke v. Bayer Corp., No. 2:19-cv-07271, 2020 WL 2048622, at *3 (C.D. Cal. Mar. 10, 2020) ("This newly acquired information must have been available to Bayer after the FDA approved the relevant label on August 19, 2010, *but before Plaintiff last used Magnevist* on

Accordingly, in considering each Plaintiff's individual claim, information that came available after that Plaintiff was last treated with docetaxel cannot constitute newly acquired information.

Next, Defendants focus on the definition of newly acquired information provided in the Code of Federal Regulations, wherein it states

> [n]ewly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.[78]

Defendants, therefore, contend that the information identified by Plaintiffs was not newly acquired information because: (1) it was previously submitted to the FDA, or (2) it did not reveal risks of a different type or greater severity or frequency than previously included in submissions to the FDA.

The regulatory pathway under which Defendants' NDAs were approved complicates this analysis. The "FDA's longstanding interpretation of section 505(b)(2) is intended to permit the pharmaceutical industry to rely to the greatest extent possible under the law on what is already known about a drug."[79] Because of the similarities between each Defendant's docetaxel and Taxotere, the FDA did not require Defendants to conduct their own toxicological or clinical studies. Rather, the FDA permitted Defendants to rely on the Agency's findings of safety and efficacy for Sanofi's Taxotere, including

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May 1, 2015.") (emphasis added); Roberto v. Boehringer Ingelheim Pharms., Inc., No. CPL-HHDCV16-6068484S, 2019 WL 4806271, at *19 n.36 (Conn. Super. Ct. Sept. 11, 2019) ("[A]n article identifying newly acquired information for the first time, but published after the patient's injury, cannot constitute newly acquired information under the CBE regulation. In that instance, there is no basis for a label change because the manufacturer would not have been able to change the label in time to prevent the injury.").

[78] 21 C.F.R. § 314.3(b).

[79] *See* Doc. 13595-3 at 3 (Woodcock Letter); Doc. 13596-3 at 3 (same); Doc. 13978-3 at 3 (same).

Taxotere's approved labeling, for the approval of their docetaxel NDAs. Thus, the language of the Warnings and Adverse Reactions sections of Defendants' docetaxel labels was based on what *Sanofi* had previously submitted to the FDA.

The extent to which these Defendants knew or had the ability to know what Sanofi had previously submitted to the FDA is unclear from the record. At the very least, this Court knows that Defendants did not have a right of reference to Sanofi's clinical trial data on which Defendants' § 505(b)(2) NDAs relied, and Defendants emphasize throughout their briefing that they did not have access to Sanofi's underlying clinical trial data at the time in question. Taking them at their word, Defendants' arguments addressing why certain information that came available post-approval was not "newly acquired information" are misleading. For example, both Accord and Hospira argue that certain scientific literature could not constitute newly acquired information because the literature did not reveal that permanent alopecia was occurring more frequently than it was in Sanofi's clinical trials. How, though, could Accord or Hospira have made this determination at the time in question if they did not have access to Sanofi's underlying clinical trial data?

This fallacious argument highlights the crux of the issue with interpreting "newly acquired information" as narrowly as Defendants propose. Without knowing the full extent of what was previously submitted to the FDA, Defendants could never determine whether information revealed risks of a different type or greater severity or frequency than included in previous submissions to the FDA. Ironically, Accord makes this argument itself, despite also relying on Sanofi's clinical trial data to prove that certain scientific literature was not newly acquired information:

> Under the FDA's regulations, information is only "newly acquired" if it is "data, analyses, or other information not previously

> submitted to" the FDA and reveals "risks of a *different type or greater severity or frequency* than previously included in submissions to FDA." 21 C.F.R. § 314.3(b) (emphasis added). This regulation implicitly requires drug manufacturers to analyze new information in context of what the manufacturer already knows about a drug—just like Sanofi did at the FDA's request in 2015. Accord lacked both the underlying clinical trial data (and thus an initial reference point) and new adverse event reports or scientific literature revealing risks of a "different type or greater severity or frequency" than those previously submitted to and considered by the FDA. It could not, for example, compare articles to Sanofi's clinical trial data, to which Accord lacked a right of reference. Consequently, while Accord implemented all of its post-market surveillance obligations by collecting, reconciling, and reporting literature and any adverse events to the FDA, nothing in the record or identified by Plaintiffs suggests that it could have initiated a CBE about permanent hair loss before Sanofi, which had the benefit of far more robust and comprehensive data.[80]

This conclusion seems nonsensical considering: (1) § 505(b)(2) manufacturers are responsible for the adequacy of their labels[81]; and (2) despite the FDA's knowledge that § 505(b)(2) NDA holders are approved in reliance on at least some information they do not have a right of reference to, the FDA still (a) made the CBE regulation available to all NDA holders, not just 505(b)(1) NDA holders[82]; and (b) does not impose on § 505(b)(2) NDA holders the duty of sameness it imposes on § 505(j) ANDA holders.

Plaintiffs, on the contrary, focus on the fact that the definition of "newly acquired information" includes "new analyses of previously submitted data," and they contend that if a drug sponsor were to determine that a warning was

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[80] Doc. 13425-4 at 22.

[81] *See Wyeth*, 555 U.S. at 570–71 ("[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It 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.") (internal citation omitted).

[82] *See* 21 C.F.R. § 314.70(c)(6)(iii) (explaining that "*the holder of an approved NDA*" may distribute its drug product after making certain changes to the label without first receiving FDA approval) (emphasis added).

insufficient based on a new analysis of previously existing data, it could submit a CBE and change its labeling.[83] To be sure, when the FDA amended the CBE regulation in 2008 to include the language that a CBE change is permissible if the change is made "to reflect newly acquired information," its notice of the final rule explained

> *if later data or analyses demonstrate that prior warnings were insufficient, such data would clearly qualify as newly acquired information under the rule*. Indeed, the rule expressly provides that new analyses of previously submitted information are considered new information that could be submitted by a CBE supplement (provided that other requirements for a CBE supplement are met). Therefore, if a sponsor determined that existing warnings were insufficient based on newly acquired information such as a new analysis of previously submitted data, the sponsor could still submit a CBE based on its new analysis of the previous data, provided the other requirements of the rule are met.[84]

"The FDA's views are 'controlling unless plainly erroneous or inconsistent with the regulation[s]' or there is any other reason to doubt that they reflect the FDA's fair and considered judgment."[85] Although Defendants propose a narrower interpretation of "newly acquired information" sufficient to justify a CBE change, this Court does not find the FDA's interpretation "plainly erroneous or inconsistent with the regulation."[86] In fact, the FDA's interpretation cures the nonsensical result Defendants' position would have produced. Accordingly, any post-approval data or analysis that would have demonstrated that the warnings in Defendants' labels were insufficient would

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[83] *See* Doc. 4407 at ¶ 147 (Second Amended Master Long Form Complaint).
[84] Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49606 (August 22, 2008) (emphasis added). In this case, "the other requirements of the rule" would be that "the evidence of a causal association satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)." *See* 21 C.F.R. § 314.70(c)(6)(iii)(A).
[85] *Mensing*, 564 U.S. at 613 (citing Auer v. Robbins, 519 U.S. 452, 461, 462 (1997)).
[86] *Auer*, 519 U.S. at 461.

have qualified as newly acquired information under the CBE regulation.

For purposes of the instant Motions, this Court assumes that the state law applicable to each Plaintiff's claim required Defendants to include the risk of permanent alopecia in their labels. Consequently, Defendants' arguments that Plaintiffs' claims are preempted if Defendants did not actually "possess" the information that could have formed the basis of the CBE change must be rejected. Unless federal law prohibited Defendants from possessing such information, the issue of whether Defendants actually "possessed" or "acquired" such information is irrelevant to the question of preemption, which asks whether it was impossible under federal law for Defendants to unilaterally add the warning state law required.[87] If there was information that Defendants *could have* acquired that would have supported a CBE change, then federal law did not prohibit Defendants from unilaterally updating their labels to include the risk of permanent alopecia.[88]

B. Availability of the CBE Regulation to Make the Change

Plaintiffs assert that if Defendants had performed proper post-marketing pharmacovigilance,

> [Defendants] would have come to the conclusion that the low threshold for a label change—"some basis to believe" there exists an "undesirable effect, reasonably associated with use of a drug"—had been met. And [they] would have done so shorty after [their] NDA[s] were approved, based on the strength of the pre-2011 evidence of a causal association.[89]

Although Plaintiffs misstate the causal association required for adverse events to be included in the Adverse Reactions section of the labeling, this Court

[87] *See Wyeth*, 555 U.S. at 569–70.
[88] See *id.* (finding that "after the first . . . incident [of Phenergan injection resulting in gangrene and an amputation] came to Wyeth's attention in 1967, it notified the FDA and worked with the agency to change Phenergan's label," but that "in later years, as amputations continued to occur, Wyeth *could have* analyzed the accumulating data and added a stronger warning about IV-push administration of the drug" (emphasis added)).
[89] Doc. 13595 at 12; Doc. 13596 at 12; Doc. 13978 at 13.

agrees that a post-approval analysis of the publicly available, pre-approval data would have demonstrated that the standard for inclusion in the Adverse Reactions section had been met.[90]

An analysis of the publicly available scientific literature, alone, would have provided some basis to believe there was a causal relationship between docetaxel and the occurrence of permanent alopecia. In January 2001, the *Journal of Clinical Oncology* published the results of a phase II, single-arm clinical trial investigating the efficacy and toxicity of docetaxel with doxorubicin and cyclophosphamide for patients with metastatic breast cancer.[91] The clinical trial involved 54 patients, and the authors reported that "the most common treatment-related nonhematologic toxicity was alopecia (87%), with long-lasting (longer than 2 years) partial alopecia in four patients."[92] In December 2006, the results of oncologist Dr. Scot Sedlacek's retrospective prospective controlled cohort study were published in *Breast Cancer Research and Treatment*. Dr. Sedlacek tracked patients treated for localized breast cancer in three groups: Group A (258 patients administered a doxorubicin and cyclophosphamide regimen without a taxane), Group B (126 patients administered doxorubicin and cyclophosphamide plus paclitaxel), and Group C (112 patients administered doxorubicin and cyclophosphamide plus docetaxel).[93] Notably, no women in Group A or Group B experienced persistent, significant alopecia, but 7 out of the 112 (6.3%) of those in Group C did.[94] In October 2010, the results of a retrospective study conducted by Dr. Hughes

[90] *See* 21 C.F.R. § 201.57(c)(7) (explaining that the Adverse Reactions section must include the adverse events "for which there is some basis to believe there is a causal association between the drug and the occurrence of the adverse event").
[91] Doc. 13857-30.
[92] *Id.*
[93] Doc. 13857-31.
[94] *Id.*

Bourgeois and others were published in *Annals of Oncology*.[95] This study involved 108 cases of persistent alopecia or suboptimal hair regrowth reported after adjuvant chemotherapy, and of the 108 cases, 96% had received a docetaxel-containing regimen.[96]

Additionally, between 2009 and 2010 there were three case reports published regarding permanent alopecia after treatment with a docetaxel-containing regimen.[97] The first report involved a retrospective evaluation of cases over the past 10 years and found that 13 women who treated at the authors' institution had been identified with permanent alopecia, and 11 of those 13 were treated with a docetaxel-based regimen.[98] The second report noted two case reports of severe and irreversible alopecia following chemotherapy with taxanes; one of the patients was treated with docetaxel and completed treatment seven years prior, and the other patient was treated with paclitaxel three years prior.[99] The third report described "a case of permanent hair loss following standard dose chemotherapy with docetaxel, carboplatin, and trastuzumab" in a patient treated for breast cancer, and the authors noted that "the lack of evidence for alopecia with trastuzumab, and the exposure to only a single infusion of standard dose carboplatin, suggests that docetaxel is the implicated agent."[100]

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[95] Doc. 13857-33 at 67; Hughes Bourgeois et al., *Long Term Persistent Alopecia and Suboptimal Hair Regrowth after Adjuvant Chemotherapy for Breast Cancer: Alert for Emerging Side Effect: French ALOPERS Observatory*, 21(8) ANNALS ONCOL. viii83 (2010).
[96] Doc. 13857-33 at 67; Bourgeois et al., *supra* note 95, at viii84.
[97] Doc. 13857-33 at 71, 72; Pat Masidonski & Suzanne Mahon, *Permanent Alopecia in Women Being Treated for Breast Cancer*, 13(1) CLIN. J. ONCOL. NURS. 13-4 (2009); Christos Prevezas et al., *Irreversible and Severe Alopecia Following Docetaxel or Paclitaxel Cytotoxic Therapy for Breast Cancer*, 160 BRIT J. DERMATOL. 881 (2009); Ben Tallon et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333 (2010).
[98] Doc. 13857-33 at 71; Masidonski & Mahon, *supra* note 97, at 13-4.
[99] Doc. 13857-33 at 72; Prevezas et al., *supra* note 97, at 881.
[100] Doc. 13857-33 at 71; Tallon et al., *supra* note 97, at 333.

Lastly, in March 2011, the same month Hospira's NDA was approved and three months before Accord and Sandoz's NDAs were approved, the results of a retrospective review conducted by Dr. Ioulios Palamaras, and others, were published in *The Journal of the American Academy of Dermatopathology*.[101] The authors reviewed the charts of 8,430 patients with non-scarring alopecia who had attended their hair clinic during the previous seven years.[102] From those records, the authors identified seven cases of PCIA and noted that five of the seven cases occurred following chemotherapy treatment with taxanes.[103]

Section 201.57(c)(7) of Title 21 of the Code of Federal Regulations contains a full explanation of what a sponsor must include in the Adverse Reactions section of the labeling:

> This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, 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.

This Court finds that Defendants could have analyzed the relevant, publicly available scientific literature discussed above, and it would have shown that there was some basis to believe there was a causal relationship between docetaxel and the occurrence of permanent hair loss. Further, because Defendants' labels contained no reference to permanent alopecia, an analysis of this scientific literature would have demonstrated that their labels were insufficient and, therefore, would have qualified as newly acquired

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[101] Doc. 13857-21.
[102] *Id.*
[103] *Id.*

information.[104] As a result, Defendants could have updated their labels via the CBE regulation.[105]

Plaintiffs further contend that as new pieces of information came available post-approval, Defendants could have analyzed the accumulating data and it would have revealed that the standard for inclusion in the Adverse Reactions section had been satisfied. This Court agrees that such an analysis would have also revealed that there was some basis to believe there was a causal relationship between docetaxel and the occurrence of permanent alopecia.

In June 2011, the histology results of the retrospective clinicopathological study conducted by Dr. Mariya Miteva, and others, were published in *The American Journal of Dermatopathology*.[106] The study involved 10 patients who developed permanent alopecia after chemotherapy. Of the 10 patients, 6 were treated for breast cancer—all with Taxotere/docetaxel alone.[107]

In May 2012, *Annals of Oncology* published the results of the retrospective study that analyzed the histological features of severe permanent alopecia in 20 breast cancer patients who were diagnosed between 2007 and 2011 after receiving treatment of a regimen including fluorouracil, epirubicin, and cyclophosphamide ("FEC") followed by Taxotere/docetaxel.[108] The study referenced the Prevezas, Tallon, and Miteva studies, which reported nine cases of permanent scalp alopecia following chemotherapy with taxanes used to treat

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[104] *See* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49606 (August 22, 2008) ("[I]f later data or analyses demonstrate that prior warnings were insufficient, such data would clearly qualify as newly acquired information under the rule.").
[105] *See* 21 C.F.R. § 314.70(c)(6)(iii)(A).
[106] Doc. 13857-36.
[107] *Id.*
[108] Doc. 13857-20.

breast cancer.[109] The authors explained that in those cases "docetaxel was almost always involved, alone in seven cases."[110] The authors likewise concluded that taxanes were probably responsible for the permanent alopecia after the FEC-docetaxel regimen as well, noting that: (1) all of the patients received taxanes (i.e., docetaxel) during the course of their treatment, but not all of them received antiestrogen or aromatase inhibitor treatment; (2) one of the patients in the study had received a full series of FEC alone for breast cancer and recalled transient but clearly reversible alopecia after the FEC treatment, but then she relapsed and was treated with the FEC-docetaxel regimen which resulted in permanent alopecia; and (3) breast cancer patients who were treated during the same time and in the same institution as the patients in this study that used the anthracycline-based regimens without concomitant or sequential taxanes were not affected by such severe, permanent scalp alopecia.[111]

In May 2013, Dr. Antonella Tosti reported two new cases of permanent alopecia following high-dose docetaxel chemotherapy for breast cancer, referencing the five previously reported in the Palamaras article, which Dr. Tosti co-authored in 2011.[112] Lastly, in December 2013, a poster abstract of a prospective clinical study was presented at the San Antonio Breast Cancer Symposium.[113] The study included 79 patients treated with a FEC-docetaxel regimen for early breast cancer between July 2005 and December 2007.[114] All patients received scalp cooling during chemotherapy, and all patients underwent a clinical examination and photographs of the scalp 5 years after

[109] *Id.*
[110] *Id.*
[111] *Id.*
[112] Doc. 13857-37.
[113] Doc. 13857-22.
[114] *Id.*

the end of chemotherapy.[115] Of the 79 patients, 26 had permanent alopecia, which was severe in 3 patients, moderate in 2 patients, and minimal in 21 patients.[116]

Thus, the post-approval scientific literature provided further evidence of the potential causal relationship between docetaxel and permanent alopecia. Accordingly, for the same reasons as above, an analysis of the accumulating data also could have formed the basis of a CBE change to the Adverse Reactions section of the label. The Court recognizes that the extent of the scientific literature that was available before each Plaintiff completed treatment with docetaxel varies. Nevertheless, whether it is the claim of Plaintiff Conley who completed treatment on January 24, 2012, or Plaintiff Cooper who completed treatment on March 23, 2015, an analysis of the scientific literature that was available at that time would have provided some basis to believe there was a causal relationship between docetaxel and the occurrence of permanent alopecia and could have formed the basis of a CBE change.

C. Individual Defenses from Defendants

Defendants' briefings are silent with respect to what a post-approval analysis of the pre-approval data, or of the accumulating data, would have shown. Instead, Defendants mainly focus on the individual pieces of evidence that came out after their NDAs were approved but before Plaintiffs were treated with docetaxel and argue why these individual pieces of data cannot constitute newly acquired information. But, as discussed above, newly acquired information is not limited to individual pieces of data; it also includes new analyses of previously submitted data.[117] This Court now turns to the

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[115] *Id.*
[116] *Id.*
[117] *See* 21 C.F.R. § 314.3(b); *see also* 73 Fed. Reg. 49601, 49606 ("Indeed, the rule expressly provides that new analyses of previously submitted information are considered new

individual arguments made by each Defendant with respect to "new analyses of previously submitted data."

i. Hospira

Hospira does not argue that an analysis of the pre-approval data would not have shown the causal association required for including adverse reactions in the labeling. Instead, Hospira argues that none of the post-approval information "triggered a re-analysis" of that data. For the reasons stated above, and reiterated again here, this Court need not address those arguments.

Whether information should have triggered a new analysis is irrelevant to the question of preemption in this matter. The Court is assuming that under state law Hospira had a duty to include a warning regarding permanent alopecia, which necessarily means that under state law Hospira had a duty to know of the risk of permanent alopecia that existed at the time. Hospira's post-marketing pharmacovigilance duties under federal law may be relevant in the future when determining whether Hospira had a duty or breached that duty under state law, but whether federal law imposed a duty to analyze the previously submitted data is irrelevant for preemption purposes.

The question for preemption in this case is whether federal law prohibited Hospira from unilaterally updating its label to include the warning Plaintiff contends state law required. Even if the federal regulations did not impose a duty on Hospira to conduct the new analysis, Hospira has not shown, and this Court is not aware, that there was any federal law that would have prohibited Hospira from doing so. Thus, the Court finds that Hospira could have conducted the analysis, and for the reasons stated above, the analysis could have formed the basis of a CBE change to Hospira's docetaxel label before Plaintiff Hickey completed treatment.

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information that could be submitted by a CBE supplement (provided that other requirements for a CBE supplement are met).").

ii. Sandoz

Sandoz argues that Plaintiff Conley "cannot assert that Sandoz possessed 'newly acquired information' in the form of 'new analyses of previously existing data that 'reveal risks of a different type of greater severity or frequency than previously included in submissions to the FDA."[118] As this Court has already explained, though, whether Sandoz possessed such information is not relevant to preemption, and so long as the new analysis would have demonstrated to Sandoz that its label was insufficient, it could have formed the basis of a CBE change. Also, to the extent Sandoz is arguing that because the individual pieces of data that came out after approval were not "newly acquired information," Sandoz had no duty under federal law to conduct the reanalysis, this Court points Sandoz to the response to Hospira's same argument above. And ultimately, for the reasons discussed extensively above, the Court finds that Sandoz could have updated its label via the CBE regulation before Plaintiff Conley completed treatment with Sandoz's docetaxel.

iii. Accord

Accord does not specifically address Plaintiffs' argument that an analysis of the pre-approval data or the accumulating data would have provided Accord with sufficient information to make a CBE change. Accord does contend that as a § 505(b)(2) manufacturer, it had access to only a fraction of the underlying clinical trial data and post-marketing data that Sanofi, as the RLD sponsor, had. Nevertheless, this Court found that the publicly available scientific literature alone was sufficient to satisfy the standard for inclusion in the labeling under 21 C.F.R. § 201.57(c) and that the post-approval scientific literature provided further evidence of a potential causal relationship between

[118] Doc. 13477-2 at 21.

docetaxel and the occurrence of permanent alopecia. Thus, regardless of whether Accord had access to Sanofi's underlying clinical trial data, the FAERS database, or Sanofi's internal adverse events database, Accord has not shown that if it had analyzed the publicly available pre-approval information or accumulating data, the analysis would not have demonstrated the insufficiency of its warnings and provided a basis for updating its label via the CBE regulation before Plaintiffs Adams, Cooper, or Woodson completed treatment with Accord's docetaxel.

As a final matter, the Court emphasizes that "impossibility preemption is a demanding defense."[119] Indeed, "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."[120] Even when Congress granted the FDA the authority to order manufacturers to revise their labels, "it reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval."[121] Defendants have failed to demonstrate that it was impossible for them to comply with both federal and state requirements. As a result, Defendants are not entitled to summary judgment based on preemption.

CONCLUSION

For the foregoing reasons, Defendant Accord Healthcare Inc.'s Motion for Summary Judgment on Preemption Grounds (Doc. 13425) is **DENIED**, Defendant Sandoz Inc.'s Motion for Summary Judgment on Preemption

[119] *Wyeth*, 555 U.S. at 573.
[120] *Id.* at 570–71.
[121] *Id.* at 571.

Grounds (Doc. 13445) is **DENIED**, and Defendant Hospira's Motion for Summary Judgment Based on Preemption (Doc. 13857) is **DENIED**.

New Orleans, Louisiana, this 2nd day of August, 2022.

JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE