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: Elizabeth Kahn, 16-17039	)	

ORDER AND REASONS

Before the Court is a Motion for Summary Judgment Based on Preemption (Doc. 11020). The Court held oral argument on the Motion on October 7, 2020. For the following reasons, the Motion is **GRANTED IN PART** and **DENIED IN PART**.

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 Inc. (collectively, "Sanofi" or "Defendants"). Plaintiffs allege that the drug caused permanent alopecia—in other words, permanent hair loss. Plaintiffs bring claims of failure to warn, negligent misrepresentation, fraudulent misrepresentation, and more. The first bellwether trial was held in September 2019, and the second trial is set for 2021.[2]

[1] Docetaxel is the generic version of Taxotere.
[2] The second trial was continued due to the COVID-19 pandemic.

Plaintiff Elizabeth Kahn, the second bellwether plaintiff, completed her Taxotere treatment in July 2008. In the instant Motion, Defendants move for summary judgment on the affirmative defense of preemption.[3] Specifically, they argue that at the time of Plaintiff's treatment, Sanofi was precluded from revising the Taxotere label that had been in effect for years. According to Sanofi, federal law prohibited the addition of stronger language to the label to warn users of a risk of permanent alopecia. Plaintiff opposes the Motion.

The History of the Taxotere Label

In 1996, the FDA approved the use of Taxotere for advanced or metastatic breast cancer. The initial labeling identified alopecia as a possible side effect of the drug and advised patients that "hair generally grows back." On August 18, 2004, the FDA approved Sanofi's supplemental New Drug Application ("sNDA") to use Taxotere in combination with two other drugs, doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan)—collectively known as "TAC"—for the adjuvant treatment of node-positive breast cancer.[4] With this sNDA, Sanofi provided the FDA the interim results of two clinical trials, TAX 316 and GEICAM 9805, as well as two articles detailing the results of two other Sanofi studies—the "Nabholtz" article and the "Sjöström" article.

In the Nabholtz article, the authors discussed the results of a Phase II clinical trial known as TAX 702.[5] The purpose of the TAX 702 trial was to "investigate[] the efficacy and toxicity of docetaxel with doxorubicin and cyclophosphamide (TAC) as first-line chemotherapy for anthracycline-naïve

[3] To the extent that Defendants raise preemption arguments relating to other Plaintiffs in the MDL, the Court will defer ruling on those arguments until a later date.
[4] Doc. 11020-2 at 3.
[5] *Id.* at 4.

patients with metastatic breast cancer."[6] The authors summarized the results of the TAX 702 study as follows:

> After an independent panel review, the overall objective response rate was 77% (complete response, 6%). Overall objective response rates in patients with visceral, bone, and liver involvement were 82%, 82%, and 80%, respectively. Median duration of response was 52 weeks, and median time to progression was 42 weeks. With a median follow-up of 32 months, the median survival had not yet been reached, whereas the 2-year survival was 57%. The main toxicities were hematologic (neutropenia grade 3/4 in 100% of patients and 95% of cycles; febrile neutropenia in 34% of patients and 9% of cycles). Documented grade 3 infection was seen in one patient (2%) in one cycle, and no toxic death was reported. Severe acute or chronic nonhematologic adverse events were infrequent, and docetaxel-specific toxicities (such as fluid retention and nail changes) were mild, with only one patient being discontinued for fluid retention. Congestive heart failure was seen in two patients (4%).[7]

In the remainder of the seven-page article, the authors more thoroughly discussed the results of the study.[8] In the following excerpt, which Sanofi highlights, the authors mentioned "long-lasting" alopecia:

> Acute nonhematologic toxicities were usually mild (Table 6) with infrequent grade 3 nausea (9%), stomatitis (6%) and diarrhea (4%). No grade 4 episodes of acute nonhematologic toxicity were reported. The most common treatment-related chronic nonhematologic toxicity was alopecia (87%), with long-lasting (longer than 2 years) partial alopecia in four patients.[9]

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[6] Doc. 11020, Ex. 26.
[7] *Id.*
[8] *Id.*
[9] *Id.*

In the second article, the "Sjöström" article, the authors described the results from a Phase III clinical trial known as TAX SI007, "which compared sequential methotrexate and 5-flurouaracil to Taxotere for the treatment of patients with advanced breast cancer."[10] The authors concluded:

> There was a significantly higher overall response rate in the docetaxel 42% (CR 8% + PR 34%) than in the MF arm 21% (CR 3% + PR 18%) (P<0.001). . . . Docetaxel also had a significantly higher response rate of 27% following crossover compared with MF (12%). Significantly more side-effects (leucopenia, infections, neuropathy, oedema, asthenia, skin, nail changes, alopecia) were seen in the docetaxel than in the MF group. However, grade 3 and 4 side-effects were infrequent with both drugs, with the exception of fatigue, alopecia and infections. . . . Based on the response rate and the primary endpoint of TTP, docetaxel is superior to sequential methotrexate and 5-fluorouacil in advanced breast cancer after anthracycline failure.[11]

In the weeks preceding the FDA's approval of the sNDA on August 18, 2004, Sanofi had proposed adding new language to the "Adverse Reactions" section of the Taxotere label.[12] Sanofi proposed adding a subsection called "Other persistent reactions."[13] The subsection mentioned, among other items, alopecia.[14] When the FDA sent Sanofi edits on the proposed language,

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[10] Doc. 11020-2 at 4.
[11] Doc. 11020, Ex. 25.
[12] *See* Doc. 11020-2 at 7–8.
[13] *Id*.
[14] The entire subsection read as follows:

> **Other persistent reactions**
> The following events were observed to be ongoing in TAC-treated patients at the median follow-up time of 55 months: alopecia (22/687), amenorrhea (133/233), neurosensory (9/73) and peripheral edema (18/112). These events were also observed in the FAC arm during the follow-up period: alopecia (9/642),

however, it had deleted the entire proposed subsection on "Other persistent reactions."[15] No reason was provided for the deletion.[16] Ultimately then, while the FDA approved a revised label to recognize this new indication of the drug, the language regarding alopecia remained the same as in the initial label.[17]

Between 2004 and 2008, the FDA approved several revised versions of the Taxotere label. Specifically, on June 30, 2004, Sanofi submitted another sNDA to the FDA.[18] The application provided for "proposed labeling changes to the package insert to incorporate the efficacy and safety information observed over the three doses evaluated in study TAX 313."[19] On March 1, 2005, Sanofi submitted a "Changes Being Effected" sNDA.[20] This application related to label language "regarding dose reduction for patients who experience stomatitis while receiving the adjuvant treatment for breast cancer."[21] On May 4, 2005, Sanofi submitted another sNDA, which involved "changes proposed to the carton, blister, active vial and diluent vial labels and the package insert to decrease the possibility of misinterpretation of the depiction of product strength.[22] The FDA approved these applications.[23]

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amenorrhea (101/186), neurosensory (2/15) and peripheral edema (3/19).

See id.; Doc. 11020, Ex. 37. This subsection related specifically to the results of the TAX 316 clinical trial. In the TAX 316 trial, 744 patients were given a Taxotere regimen that included Taxotere, Adriamycin, and cyclophosphamide. *See* Doc. 11332. Researchers called this the "TAC" arm of the study. The other arm of the study was a control/comparator arm—the "FAC" arm. In this arm, patients received a chemotherapy agent called Fluorouracil instead of Taxotere. Participants were followed for 10 years after their treatment. During this period, researched tracked ongoing adverse events, including alopecia.

[15] Doc. 11020-2 at 7–8.
[16] *Id.*
[17] *See id.*
[18] Doc. 11020, Ex. 62.
[19] *Id.*
[20] Doc. 11020, Ex. 63.
[21] *Id.*
[22] Doc. 11020, Ex. 64.
[23] *Id.*; Doc. 11020, Ex. 62; Doc. 11020, Ex. 63.

On September 23, 2005, Sanofi submitted another sNDA.[24] This one "provide[d] for the use of Taxotere (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease."[25] The FDA approved the application along with the labeling text that related to the new use.[26]

On December 21, 2005, Sanofi submitted another "Changes Being Effected" sNDA.[27] This one "provide[d] for changes to the package insert Black Box Warning and WARNINGS, Hypersensitivity Reactions subsection to include a new warning for severe hypersensitivity reactions and to add four new sections to the ADVERSE REACTIONS, Post-Marketing Experiences subsection."[28] On April 14, 2006, Sanofi submitted another sNDA, which "provide[d] for the use of TAXOTERE® (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN)."[29] On March 29, 2007, Sanofi submitted another sNDA, which "provide[d] for the use of TAXOTERE® (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)."[30] The FDA approved these applications along with revised labeling text.[31]

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[24] Doc. 11020, Ex. 65.
[25] *Id.*
[26] *Id.*
[27] Doc. 11020, Ex. 66.
[28] *Id.*
[29] Doc. 11020, Ex. 67.
[30] Doc. 11020, Ex. 68.
[31] *See id.*; Doc. 11020, Ex. 66; Doc. 11020, Ex. 67.

Plaintiff Kahn received her treatment in 2008 after the FDA's approval of these revisions to the Taxotere label. None of these revisions, however, related to alopecia. In 2008, then, when Kahn was treated, the FDA-approved label provided, as it had since 1996, that "[l]oss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back."[32]

In early 2015, MDL Plaintiff Kelly Gahan contacted the FDA about her experience with Taxotere.[33] She told the FDA about her hair loss, and the FDA agreed to open an investigation into permanent alopecia.[34] After this, Gahan encouraged others to email the FDA with stories of their permanent hair loss, and the FDA received correspondence from more than 40 patients about permanent alopecia.[35] For example, one patient wrote that her "life has been ruined" and she "was never warned of this possible side effect."[36] Another wrote, "I feel that I should have been warned of this possible side effect."[37]

On March 23, 2015, the FDA contacted Sanofi requesting "a summary of cases of permanent partial or total alopecia associated with docetaxel use."[38] On April 10, 2015, Sanofi responded to the FDA by submitting a 25-page analysis.[39] The analysis included a review of 2,118 cases of alopecia from Sanofi's pharmacovigilance database; a chart of reports of long-standing

[32] *See* Doc. 11020-2 at 2–3, 16.
[33] *Id.* at 24–25.
[34] *Id.*
[35] *Id.* at 25–26.
[36] Doc. 11020-2 at 26.
[37] *Id.*
[38] Doc. 11020, Ex. 116.
[39] Doc. 11020, Ex. 118.

alopecia associated with Taxotere use; a summary of the alopecia data from GEICAM 9805; and Sanofi's overall analysis of the potential side effect.[40]

On October 2, 2015, after reviewing this submission, the FDA requested additional information on permanent alopecia.[41] The FDA further requested that Sanofi update its label, "due to the possibility that permanent alopecia may be associated with docetaxel use."[42] Specifically, the FDA asked Sanofi to "[a]mend the package insert in Section 6.2 (Postmarketing Experience) (and patient information, if appropriate) to add information on permanent or irreversible alopecia."[43] Soon after this, on October 13, 2015, Senator Mark Warner wrote to the FDA after hearing from a constituent who told him that "[f]or over a decade, the breast cancer drug Taxotere has been leaving women permanently bald or with severe male pattern baldness."[44] The Senator asked that the FDA investigate and provide him with a response.[45] Around the same time, the FDA noted in its internal correspondence regarding Taxotere, that "virtually all of the described cases of alopecia were confounded by use of other cytotoxic agents, which are also known to cause alopecia."[46]

In response to the FDA's request, Sanofi sent the FDA a "Changes Being Effected" labeling supplement.[47] Sanofi informed the FDA that "additions of permanent alopecia have been made" to three parts of the Taxotere label:

- Subsection 6.2 Post-Marketing Experiences
- Section 17 PATIENT COUNSELING INFORMATION

[40] *Id.*; Doc. 11020-2 at 25.
[41] *See* Doc. 11214-94 at 2.
[42] Doc. 11020, Ex. 135.
[43] *See* Doc. 11214-94 at 2.
[44] Doc. 11020, Ex. 126. Notably, Plaintiff Gahan encouraged others suffering from permanent hair loss to contact their Congressional representatives and request a change to the Taxotere label. Doc. 11020-2 at 27.
[45] *Id.*
[46] Doc. 11020, Ex. 135.
[47] *See* Doc. 11214-94 at 2.

- "What are the possible side effects of TAXOTERE?" of Patient Information.[48]

Notably, in Section 6.2, Sanofi included the following sentence: "Cases of permanent alopecia have been reported."[49] Informed by the data Sanofi submitted, the FDA concluded that "[Sanofi's] simple statement that permanent cases have been reported is all that can reliably be said given the tremendous limitations of the available data."[50]

LEGAL STANDARD

"Federal preemption is an affirmative defense that a defendant must plead and prove."[51] The doctrine of preemption derives from the 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."[52] Where state and federal law are in direct conflict with each other, "state law must give way."[53] Known as impossibility preemption, this is "a demanding defense," requiring a defendant "to demonstrate that it was impossible to comply with both federal and state requirements."[54]

A preemption analysis must be guided by the two cornerstones of preemption jurisprudence.[55] First, a court should consider "the purpose of Congress."[56] Second, in all preemption cases, a court must assume "that the

[48] *Id.*
[49] Doc. 11020, Ex. 136.
[50] Doc. 11020, Ex. 135.
[51] Fisher v. Halliburton, 667 F.3d 602, 609 (5th Cir.2012) ("Federal preemption is an affirmative defense that a defendant must plead and prove.").
[52] U.S. CONST. art. VI, cl. 2.
[53] PLIVA, Inc. v. Mensing, 564 U.S. 604, 617 (2011).
[54] *See* Wyeth v. Levine, 555 U.S. 555, 573 (2009).
[55] *Id.* at 565.
[56] *Id.* (internal citations omitted).

historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."[57]

LAW AND ANALYSIS

I. The Parties' Arguments

Sanofi argues that Plaintiff's state law failure to warn claim is preempted by federal law. The law at issue is the Food, Drug, and Cosmetic Act of 1983 (the "FDCA") as well as the FDA regulations promulgated pursuant to it. Sanofi asserts that, pursuant to the FDCA, once the FDA approved its label for Taxotere, Sanofi could not later unilaterally change the label to include additional warnings. Sanofi argues that to make such a unilateral change, the regulations require "newly acquired information," or information not previously submitted to the FDA. Sanofi emphasizes that Plaintiff points to no "newly acquired information." According to Sanofi, then, because the label in effect at the time of Plaintiff's treatment was approved by the FDA, Defendants have carried their burden on preemption.

Sanofi urges the Court to apply a burden-shifting, four-part test enunciated in *Ridings v. Maurice*, No. 15-cv-00020, 2020 WL 1264178 (W.D. Mo. Mar. 16, 2020). Under this proposed analysis, a plaintiff would first identify the specific warning that the defendant allegedly failed to give. The burden would then shift to the defendant who must show that the warning it did provide complied with federal law. If this showing is made, the plaintiff must produce "newly acquired information" showing that the defendant could have unilaterally revised its label without FDA approval. If the plaintiff does this, the defendant then bears the burden of coming forward with "clear

[57] *Id.* (internal citations omitted).

evidence" showing that the FDA, even if presented with new evidence, would have rejected the warning advocated by the plaintiff.

In response, Plaintiff argues that *Ridings* is misguided and that Sanofi erroneously places the burden of disproving preemption largely on Plaintiff. Plaintiff cites the recent Supreme Court decision, *Merck Sharp & Dohme Corp. v. Albrecht*, and avers that the burden is on the manufacturer to show that (1) "it fully informed the FDA of the justifications for the warning required by state law," and (2) "the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning."[58]

II. The Court's Analysis

As instructed by the Supreme Court, this Court begins by considering "the purpose of Congress."[59] As the Court explained in *Wyeth v. Levine*, Congress enacted the FDCA in the 1930s.[60] The FDCA required every manufacturer to submit a "new drug application" to the FDA for review.[61] In the application, a manufacturer had to include reports of investigations and "specimens of proposed labeling."[62] Until an application became effective, a manufacturer could not distribute a drug.[63] If the FDA determined that a drug was not safe to use as labeled, the FDA could reject an application.[64] If the FDA failed to act on an application, it became effective 60 days after being filed.[65]

[58] Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1678 (2019).
[59] *See Levine*, 555 U.S. at 573.
[60] *Id.* at 566.
[61] *Id.*
[62] *Id.*
[63] *Id.*
[64] *Id.*
[65] *Id.*

In 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer.[66] Under this framework, instead of the FDA proving harm to keep a drug off the market, the manufacturer had to show that its drug was "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" before distributing the drug.[67] In these amendments, "Congress took care to preserve state law."[68] The amendments included a clause "indicating that a provision of state law would only be invalidated upon a 'direct and positive conflict' with the FDCA."[69] As the Eastern District of Louisiana has noted, "Congress has demonstrated a clear intent to preserve the functions of both the FDA and state tort remedies," and courts should "protect that balance."[70]

In 2007, Congress again amended the FDCA, granting the FDA "statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval."[71] In doing so, Congress did not require the FDA to preapprove all changes to drug labels.[72] Instead, Congress made clear that manufacturers "remain responsible for updating their labels."[73]

This 2007 amendment led to the "Changes Being Effected" ("CBE") regulation.[74] Under the current CBE regulation, a manufacturer may make "[c]hanges in the labeling to reflect newly acquired information" without prior FDA approval, if the change is "[t]o add or strengthen a contraindication,

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[66] *Id.* at 567.
[67] *Id.*
[68] *Id.*
[69] *Id.*
[70] In re Xarelto (Rivaroxaban) Prods. Liab. Litig., 2017 WL 3188456, at *4 (E.D. La. July 21, 2017).
[71] *Levine*, 555 U.S. at 567.
[72] *Id.*
[73] *Id.* at 568.
[74] *Id.* at 567–68.

warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)."[75] "Newly acquired information" is defined to include "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses)."[76]

The Court now turns to Plaintiff's claim. Plaintiff Kahn brings her failure to warn claim under the Louisiana Products Liability Act ("LPLA").

> The language of the LPLA provides that a plaintiff may prevail on her failure to warn claim if "[1] the product possessed a characteristic that may cause damage and [2] the manufacturer failed to use reasonable care to provide an adequate warning of such characteristic and its danger to users and handlers of the product."[77]

Here, Plaintiff alleges that "Defendants failed, and some still fail, to warn that permanent or irreversible hair loss is a common side effect" of Taxotere.[78] The Master Complaint goes on to describe the CBE regulation.[79]

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[75] 21 C.F.R. § 314.70(c)(6)(iii).
[76] *Id.* § 314.3.
[77] Grenier v. Med. Eng'g Corp., 243 F. 3d 200, 205 (5th Cir. 2001) (quoting LA. REV. STAT. ANN. § 9:2800.57).
[78] Doc. 4407 at 3. Sanofi argues that Plaintiff must identify the specific warning that Sanofi allegedly should have provided. In support of this, Sanofi cites the previously mentioned *Ridings* case, 444 F. Supp. 3d 973, a United States Magistrate Judge opinion from the Western District of Missouri. The Court is not bound by this opinion, nor does the Court find it persuasive. Instead, the Court finds that Plaintiff Kahn has no obligation to craft the specific warning that Sanofi allegedly should have provided. Louisiana cases suggest that she must only articulate how the label was inadequate, which she has done. *See* Dendinger v. Covidien LP, Civil Action No. 18-4168, 2018 WL 4462579, at *3 (E.D. La. Sept. 18, 2018) (finding that to allege inadequate warning claim under the LPLA, plaintiff must at least mention specific risks that were not disclosed); Jacobsen v. Wyeth, LLC, Civil Action No. 10-0823, 2012 WL 3575293, at *6 (E.D. La. Aug. 20, 2012) ("[A] plaintiff must prove the language of the warning was inadequate to reasonably inform the recipient about the nature of the danger involved."). In addition to this, given that Sanofi never attempted a CBE change to warn of permanent alopecia, the exact language of any hypothetical warning is irrelevant. If Sanofi had attempted a CBE change and been rejected, Plaintiff would perhaps then need to specify what language she alleges Sanofi should have used.
[79] Doc. 4407 at 28.

Defendants argue that the label in effect in 2008 was approved by the FDA and that Sanofi could not strengthen the label to comply with state law as Plaintiff alleges. Defendants emphasize that to receive approval in 2004 for the adjuvant use of Taxotere, Sanofi provided the FDA with the results of two clinical trials as well as the Nabholtz and Sjöström articles. According to Sanofi, these sources "disclosed data and reports of alopecia, including reports of patients with ongoing, persistent, or nonreversible alopecia following treatment with combination chemotherapy regimens that included Taxotere."[80] Because Sanofi provided all of this information to the FDA, Sanofi avers that Plaintiff can point to no "newly acquired information" justifying a CBE change before 2008.

Sanofi focuses on whether "newly acquired information" existed between 2004 and 2008.[81] While the Court agrees that the existence of "newly acquired information" is the appropriate question, the critical issue is how "newly acquired information" is defined. According to Sanofi, providing the FDA with alopecia data, together with a wealth of other data, was enough to fulfill Sanofi's obligations. In *Levine*, however, the Supreme Court makes clear that a manufacturer must analyze the accumulating data—including any pertinent data that predated supplemental applications—for the FDA.

In *Levine*, the plaintiff, Diana Levine, went to a local clinic seeking treatment for a migraine headache as well as nausea.[82] To treat her nausea, a physician assistant administered Phenergan to Levine by using the "IV-push

[80] Doc. 11020-1 at 8.

[81] The Court notes that at oral argument, Sanofi argued that the Court should limit its consideration of "newly acquired information" from 2007, the date of the last sNDA, until 2008, the date of Plaintiff Kahn's infusion. Sanofi's briefing, however, focuses on the time from 2004 until 2008.

[82] *Levine*, 555 U.S. at 559.

method," whereby the drug is injected directly into a patient's vein.[83] Somehow, the Phenergan entered the plaintiff's artery, either because the needle penetrated an artery directly or because the drug escaped from the vein into surrounding tissue.[84] As a result, the plaintiff developed gangrene, leading doctors to amputate her entire forearm.[85]

In its opinion, the Supreme Court discussed the history of Phenergan, explaining that the FDA first approved "injectable Phenergan" in 1955.[86] In 1973 and 1976, the manufacturer submitted supplemental applications to the FDA, which the FDA approved after proposing labeling changes.[87] In 1986, the manufacturer submitted another application to the FDA, and for the next 17 years, the manufacturer and the FDA "intermittently corresponded about Phenergan's label."[88] Despite this history, when the Supreme Court was determining whether "newly acquired information" existed, the Court did not limit its focus to new reports that arose after the supplemental applications. Instead, the Court noted that there were "at least 20 reports of amputations similar to Levine's *since the 1960's*."[89] The Court further noted that when the first amputation occurred in 1967, the manufacturer, Wyeth, "notified the FDA and worked with the agency to change Phenergan's label."[90] Still, the Court wrote that "as amputations continued to occur, Wyeth *could have analyzed the accumulating data* and added a stronger warning about IV-push administration of the drug."[91] The Court, then, appeared to consider what

[83] *Id.*
[84] *Id.*
[85] *Id.*
[86] *Id.* at 561.
[87] *Id.*
[88] *Id.*
[89] *Id.* at 562–63, 569 (emphasis added).
[90] *Id.* at 569.
[91] *Id.* at 570.

information was available for analyses since the drug's "initial approval" in 1955.[92] The Court did not assume that in those 17 years of intermittent correspondence about the Phenergan label, the FDA, on its own initiative, considered whether to strengthen any warning about the risks of administering Phenergan using the "IV-push" method.

As previously discussed, Sanofi submitted an application in 2004 for the use of Taxotere in the adjuvant treatment of node-positive breast cancer. Along with the application, Sanofi provided the FDA with the results of two clinical trials as well as the Nabholtz and Sjöström articles. Although Sanofi claims that these sources clearly disclosed information regarding persistent alopecia, the only sentence that Sanofi highlights for the Court is this one, which comes from the seven-page Nabholtz article: "The most common treatment-related chronic nonhematologic toxicity was alopecia (87%), with long-lasting (longer than 2 years) partial alopecia in four patients."[93]

When Sanofi submitted its sNDA to the FDA in 2004, there was no attempt to alert the FDA of an uptick in reports of permanent alopecia, and the Court will not assume that the FDA analyzed whether there was any such uptick. According to the case law, a manufacturer bears an ongoing responsibility to update its label; this responsibility is not on the FDA.[94] As the *Levine* Court noted, "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks

[92] *Id.* at 567 (noting that in 2007, Congress gave the FDA authority to require a manufacturer to change its drug label "based on safety information that becomes available after a drug's initial approval").
[93] Doc. 11020-2 at 4.
[94] *See Levine*, 555 U.S. at 570–71 ("[I]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times.").

emerge."[95] Thus, while the underlying data may have been there in 2004, Sanofi did not analyze or highlight the relevant data in any way for the FDA.

The Court notes that in 2004 the FDA did delete a subsection that Sanofi proposed to add to the Taxotere label. This subsection, called "Other persistent reactions," described the results of the TAX 316 clinical trial, and it mentioned alopecia among other items. The FDA, however, provided no reason for the deletion. Without more, this Court cannot divine the FDA's reason for removing this entire subsection, and the Court will not interpret the deletion as a pronouncement about permanent alopecia.

Even after 2004, Sanofi made no attempt to alert the FDA of any uptick in reports of permanent alopecia. This is supported by the fact that in 2015, the FDA asked *Sanofi* to analyze permanent alopecia.

Considering the evidence, the Court finds that, like the manufacturer in *Levine*, Sanofi "could have analyzed the accumulating data" prior to Kahn's treatment and used the CBE process to unilaterally strengthen its label.[96] The evidence shows that in 2006, a physician asked Sanofi "if there was any documentation/knowledge about the reversibility of alopecia after Taxotere treatment (e.g., expected time frame)."[97] He noted that his patient had suffered alopecia since 2004.[98] In Sanofi's internal communications about this question, one of Sanofi's Global Safety Officers writes: "Only peripheral knowledge. I know that there were some irreversible cases of alopecia as documented in the clinical trials."[99] Rather than suggesting an investigation, however, she writes

[95] *Id.* at 578–79.
[96] *Id.* at 569–70 ("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.").
[97] Doc. 11214-36 at 3.
[98] *Id.*
[99] *Id.* at 2.

this: "This is the kind of thing that a noncompany physician would review in their practice and possibly report in the literature--however, I am NOT advising a lit search for this topic!"[100] This evidence suggests that Sanofi chose to ignore the accumulating data rather than investigate and analyze it.

Plaintiff has shown that if Sanofi had analyzed the information available between 2004 and 2008, the information would have revealed the risk of permanent alopecia. As the *Levine* Court noted, if a manufacturer submits adverse event information to the FDA, "then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA," this meets the requirement for "newly acquired information."[101]

Plaintiff relies on a certain analysis conducted by an oncologist named Dr. Scot Sedlacek. She argues that this analysis could have supported a CBE change. As the Master Complaint describes, Dr. Sedlacek presented a study at a breast cancer conference in 2006.[102] His study was titled "Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide (AC) chemotherapy in women with breast cancer."[103] Sanofi argues that Dr. Sedlacek's work cannot constitute "newly acquired information" because it does not "reveal risks of a different type or greater severity or frequency than previously included in submission to the FDA" as the CBE regulation provides.[104] Sanofi emphasizes that the interim results of TAX 316, for example, reported that 3.2 percent of TAC patients

[100] *Id.*
[101] *Levine*, 555 U.S. at 569.
[102] Doc. 4407 at 29.
[103] *Id.*
[104] Doc. 11020-1 at 11 (quoting 21 C.F.R. § 314.3).

suffered "alopecia ongoing into the follow-up period."[105] Dr. Sedlacek's work, according to Sanofi, revealed nothing the FDA did not already know.

Sanofi's argument misses the point. Preemption is a "demanding defense."[106] It is not enough for Sanofi to show that the adverse event reports had been submitted to the FDA. Sanofi had an obligation to analyze those reports for the FDA. It appears to this Court that Sanofi is attempting to shift the responsibility of analyzing these reports to the FDA. Indeed, the FDA ultimately had to ask Sanofi to do the requisite analysis in 2015.

As this Court has noted in prior rulings, the primary objective of TAX 316 was to evaluate survival rates, not the occurrence of alopecia.[107] Similarly, when Sanofi submitted data to the FDA in 2004, the focus was not on alopecia. Nothing suggests that in 2004 Sanofi drew the FDA's attention to the rates of ongoing alopecia. The Sedlacek presentation, however, focused on alopecia, and this presentation was in 2006—the same year that Sanofi was internally avoiding a "lit search," or an investigation, of permanent alopecia. The Court also finds it significant that the FDA contacted Sanofi in 2015 and requested an analysis of permanent alopecia. Contrary to what Sanofi argues, the data on permanent alopecia was apparently accumulating in the years before 2015, and the FDA was not recognizing it. Indeed, as the *Levine* Court wrote, "[t]he FDA has limited resources to monitor the 11,000 drugs on the market."[108] Sanofi was in a better position to analyze the risks of its drug, but the evidence suggests that Sanofi was choosing not to do so.

Considering the limitations of the data Sanofi provided to the FDA in 2004, the Sedlacek presentation, which centered around the risk of persistent

[105] *Id.*
[106] *See Levine*, 555 U.S. at 573, 578.
[107] *See* Doc. 11332.
[108] *See Levine*, 555 U.S. at 578–79.

alopecia, would have "reveal[ed] risks of a different type or greater severity or frequency than previously included in submission to the FDA."[109] The Sedlacek presentation, therefore, constituted "newly acquired information," and it was enough to support a CBE change.

The Court's analysis, however, does not end here. According to Supreme Court precedent, if a manufacturer can show "clear evidence" that the FDA would not have approved a change to the label, this "pre-empts a claim, grounded in state law, that a drug manufacturer failed to warn consumers of the change-related risks associated with using the drug."[110] To show "clear evidence," a manufacturer must show that it "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."[111] Whether "clear evidence" exists is a question of law for the judge to decide, and the Supreme Court has guided judges to "simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflict.'" [112] A hypothetical or potential conflict is insufficient to preempt a state statute.[113]

The Court finds that Sanofi has met the "clear evidence" standard as it relates to the placement of the warning. The evidence shows that in 2015, the FDA worked closely with Sanofi to assess the risk of permanent alopecia. At that time the FDA was "fully informed" of the justifications for a warning, and the FDA specifically advised Sanofi to warn of permanent alopecia in certain parts of its label. In response, Sanofi warned of permanent alopecia in the

[109] *Levine*, 555 U.S. at 569.
[110] *Albrecht*, 139 S. Ct. at 1672.
[111] *Id.*
[112] *Id.* at 1679.
[113] *See id.*

"Adverse Reactions" section of the label, and the FDA approved this. Years later, in 2018, a plaintiff in this MDL, Dr. Kelly Gahan, requested that a "Black Box" warning for permanent alopecia be added to the Taxotere label.[114] The FDA rejected her request and explained that "FDA officials determined that the appropriate place for the possible permanent alopecia is in Section 6.2 Postmarketing Experience, and in Section 17 Patient Counseling Information of the Taxotere label."[115] There is "clear evidence" then that the FDA would not have approved of placing a warning in the more serious "Warnings and Precautions" section of the label.[116] To the extent Plaintiff alleges that Sanofi should have done so before Kahn was treated, her claim is preempted.

There is no "clear evidence," however, showing that the FDA would have rejected a warning of permanent alopecia in the "Adverse Reactions" section of the label prior to Kahn's treatment. The evidence shows that before Kahn was treated, Sanofi never "fully informed" the FDA of the justifications for a warning regarding permanent alopecia. When Sanofi submitted data to the FDA in 2004, Sanofi's goal was to expand the distribution of its drug; it was not to correspond with the FDA about whether the Taxotere label should warn of permanent alopecia.

The Court finds it telling, too, that the FDA in 2015 had to ask Sanofi for information on the risk of permanent alopecia. The Third Circuit faced similar facts in *In re Avandia Marketing, Sales & Prods. Liab. Litig.*, 945 F.3d 749, 754, 758–59 (3d Cir. 2019). In *Avandia*, the manufacturer had submitted a "Prior Approval Supplement" to the FDA and proposed new label language

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[114] Doc. 9268-2 at 13.
[115] *Id.*
[116] The Court notes, too, that a "black box" warning is "the strongest type of warning allowed in drug labeling, and to ensure their significance is undiluted, use of a black box warning is permitted only where specifically required by the FDA." Amos v. Biogen Idec Inc., 249 F. Supp. 3d 690, 694 (W.D.N.Y. 2017).

warning of cardiac risks.[117] Upon review, the FDA found that the information submitted was inadequate and that further analysis was required.[118] The FDA then directed the manufacturer to provide additional information.[119] In considering whether the manufacturer had "fully informed" the FDA of the justifications for a warning, the Third Circuit found it significant that the original submission of information was inadequate and that the FDA requested more data.[120]

Similarly, here, in 2015, the FDA had to contact Sanofi and ask for an analysis of permanent alopecia. The evidence shows that the FDA learned from third-party sources, rather than from Sanofi, about the risk of permanent alopecia. Then, upon review of the information Sanofi initially provided, the FDA asked Sanofi for more information. All of this suggests that Sanofi was sitting on its hands rather than making an "earnest attempt" to keep the FDA informed of the possible need for a stronger warning.[121] Certainly, the FDA was not "fully informed" in the years preceding 2015; otherwise, the FDA would not have had to ask Sanofi for an analysis. Accordingly, because there is no clear evidence showing the FDA before 2008 was "fully informed" and would have rejected a warning in the "Adverse Reactions" section of the Taxotere label, the remainder of Plaintiff's claim is not preempted.

CONCLUSION

For the foregoing reasons, the Motion for Summary Judgment Based on Preemption (Doc. 11020) is **GRANTED IN PART** and **DENIED IN PART**.

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[117] *Avandia*, 945 F.3d at 753–54.
[118] *Id.*
[119] *Id.*
[120] *Id.* at 758.
[121] *See Levine*, 555 U.S. at 561; *Xarelto*, 2017 WL 1395312, at *4.

New Orleans, Louisiana this 18th day of December, 2020.

JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE