UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

MICHAEL KRANTZ, INDIVIDUALLY, AND ON BEHALF OF THE ESTATE OF JANIS KRANTZ, DECEASED, LAUREN GREGORY, AND JOSHUA KRANTZ,

Plaintiffs,

v.

REGENERON PHARMACEUTICALS, INC. and SANOFI AVENTIS US, LLC,

Defendants.

Case No. 2:23-cv-08034-WLH-MRW

ORDER RE DEFENDANTS' MOTION TO DISMISS [24] AND REQUEST FOR JUDICIAL NOTICE [24-1]

This matter comes before the Court on Defendants Regeneron Pharmaceuticals, Inc. and Sanofi-Aventis U.S. LLC's (collectively the "Defendants") Motion to Dismiss Complaint (the "Motion"), dated November 3, 2023, (Mot. to Dismiss, Docket No. 24) and concurrently filed Request for Judicial Notice ("RJN") (RJN, Docket No. 24-1). Plaintiffs Michael Krantz, individually and on behalf of the estate of Janis Krantz ("Mrs. Krantz"), Lauren Gregory, and Joshua Krantz (collectively the "Plaintiffs") filed their Opposition to Defendants' Motion (the "Opposition") and RJN on November 24, 2023. (Docket No. 31). Defendants filed their Reply in Support of

their Motion (the "Reply") on December 1, 2023. (Docket No. 34). This matter is fully briefed.

On December 15, 2024, the Court held oral arguments and heard from all parties. After considering the parties' arguments and submitted evidence, and for the reasons discussed below, the Court **GRANTS** Defendants' RJN (Docket No. 24-1), **GRANTS** Plaintiffs' request for judicial notice (Docket No. 31)[1], and **DENIES** Defendants' Motion (Docket No. 24).

I. BACKGROUND

A. Relevant Parties

Defendants are manufacturers and marketers of Libtayo. (Compl., Docket No. 1 ¶ 14). Plaintiff, Mrs. Krantz, was a 73-year-old woman who is alleged to have suffered a fatal adverse drug reaction to Libtayo. (*Id.* ¶ 8). Plaintiff Michael Krantz is the spouse and administrator of the estate of the decedent, Mrs. Krantz. (*Id.* ¶ 1). Plaintiffs Joshua Krantz and Lauren Gregory are the adult children of the decedent. (*Id.* ¶¶ 2, 3).

B. Factual Background

This is a product liability matter involving the product labeling of the cancer drug Libtayo. (*Id.* ¶ 9). Libtayo is a prescription skin cancer treatment drug used to treat a type of skin cancer called cutaneous squamous cell carcinoma ("CSCC"). (Docket No. 24-10 at 31). Mrs. Krantz's physician, Dr. Nilesh Vora, prescribed Libtayo to Mrs. Krantz on April 11, 2022. (Docket No. 1 ¶¶ 16, 71). In evaluating Libtayo as a potential treatment option, Dr. Vora relied on, among other thing, "the branded U.S. Libtayo label." (*Id.* ¶ 72).

On April 18, 2022, Mrs. Krantz developed several medical issues including

[1] Plaintiffs did not file a motion seeking judicial notice. Rather, in a footnote contained within their Opposition, Plaintiffs opposed Defendants' RJN and argued in the alternative that if the Court took judicial notice of Defendants' exhibits, the Court should likewise take notice of Plaintiffs' exhibits. As discussed further below, *infra* III.A–B, the Court grants Plaintiffs' request.

malaise, diffuse rash, and swelling of the left side of her face, and sought medical care at Long Beach Memorial Care. (*Id.* ¶ 16). After being evaluated and treated by physicians at different medical facilities over the course of three weeks, Mrs. Krantz was diagnosed with Stevens-Johnson Syndrome ("SJS") and toxic epidermal necrolysis ("TEN"). (*Id.* ¶¶ 16–20). Mrs. Krantz ultimately succumbed to her illness and died on April 30, 2022. (*Id.*). Her death certificate noted that the primary cause of her death was due to SJS and TEN caused by "CPI therapy (Libtayo)." (*Id.* ¶ 20).

i. *FDA Approval and Labels*

Libtayo is part of a class of drugs known as PD-1/PD-L1 inhibitors. (Docket No. 1 ¶ 10, n.1). The FDA approved Libtayo as a treatment for advanced CSCC on September 28, 2018. (Docket No. 24-3, Exh. A). As part of Defendants' FDA application for Libtayo's approval, Defendants submitted a report, that analyzed the immune-mediated adverse reactions reported in Libtayo's clinical trials. (Docket No. 24-4, Exh. B). This report included information about two patients who had experienced similar fatal skin adverse reactions, including one patient who experienced the same SJS and TEN reactions. (*Id.*).

Libtayo's 2021 label, which is the relevant label that was in effect in the United States when Mrs. Krantz was prescribed the drug and at the time of her death, stated two warnings about adverse reactions related to SJS and TEN. The first reference is under a section entitled "Recommended Dosage Modifications for Adverse Reactions" and reads in relevant part:

Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[b]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue

(Docket No. 24-10; Exh. H at 5).

The second reference is contained in a section entitled "Warnings and Precautions: Severe and Fatal Immune-Mediated Adverse Reactions" and reads in

relevant part:

> Immune-Mediated Dermatologic Adverse Reactions
>
> LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue LIBTAYO depending on severity *[see Dosage and Administration (2.3)]*.
>
> Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.
>
> Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reinitiated LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

(*Id.* at 9)

C. Procedural History

On September 26, 2023, Plaintiffs filed the instant matter. The Complaint alleges the following four causes of action: (1) strict products liability/failure to warn; (2) negligence; (3) negligent misrepresentation; and (4) gross negligence. (*See generally* Compl., Docket No. 1). Specifically, Plaintiffs alleges six inadequacies with Defendants' labeling: "i) that Libtayo causes SJS and TEN and that cases of SJS and TEN occurred in patients taking the drug; ii) that there is an increased risk of SJS/TEN from Libtayo beyond what is disclosed in the U.S. label; iii) about frequency or incidence data that would allow U.S. prescribing physicians to place the increased risk of SJS/TEN in context when assessing the risk-benefit profile of Libtayo against safer and more efficacious drugs; iv) that cases of SJS/TEN (including fatal cases) occurred in Libtayo clinical trials; v) that certain subpopulations including those occupied by Mrs. Krantz (females) are at an increased risk of SJS and TEN; or vi) that patients receiving Libtayo should be subject to strict medical monitoring for the early

signs of SJS/TEN and warned to seek specialized medical treatment at the first sign of these reactions." (*Id.* ¶ 9).[2]

On November 3, 2023, Defendants filed the instant Motion. (Docket No. 24). Defendants' Motion seeks to dismiss Plaintiffs' Complaint on two grounds: (1) Libtayo's drug label adequately warns of the effects of SJS and TEN as a matter of law; and (2) the affirmative defense of preemption. (*See generally id.*). Defendants concurrently filed a RJN asking the Court to take notice of 22 exhibits, which include documents from the Food and Drug Administration ("FDA") and scientific articles. (Docket Nos. 24-1, 24-3–24). On November 24, 2023, Plaintiffs filed its Opposition. (Docket No. 31). On December 1, 2023, Defendants filed their Reply. (Docket No. 34).

II. LEGAL STANDARD

Pursuant to Fed. R. Civ. P. 8(a), a "pleading that states a claim for relief must contain… a short and plain statement of the claim showing that the pleader is entitled to relief." The complaint must state facts sufficient to show that a claim for relief is plausible on its face. *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555 (2007). The complaint need not include detailed factual allegations but must provide more than just a "formulaic recitation of the elements of a cause of action." *Id.* at 555.

Under Fed. R. of Civ. P. 12(b)(6), a party may move to dismiss a cause of action for failure to state a claim upon which relief can be granted. A complaint may be dismissed for failure to state a claim for one of two reasons: (1) lack of a cognizable legal theory; or (2) insufficient facts under a cognizable legal theory. *Id.*; *see also Mendiondo v. Centinela Hosp. Med. Ctr.*, 521 F.3d 1097, 1104 (9th Cir. 2008).

"To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'"

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[2] Plaintiffs refer to these inadequate warnings collectively as the "Krantz Warnings." For ease of reference, the Court will do the same.

Ashcroft v. Iqbal, 556 U.S. 662, 678 (2009) (quoting *Twombly*, 550 U.S. at 570). The court must construe the complaint in the light most favorable to the plaintiff, accept all allegations of material fact as true, and draw all reasonable inferences from well-pleaded factual allegations. *Gompper v. VISX, Inc.*, 298 F.3d 893, 896 (9th Cir. 2002). The court is not required to accept as true legal conclusions couched as factual allegations. *See Iqbal*, 556 U.S. at 678. "A claim has facial plausibility when the plaintiff pleads factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Id.*

III. REQUEST FOR JUDICIAL NOTICE

On a motion to dismiss, the Court may consider "only allegations contained in the pleadings, exhibits attached to the complaint, and matters properly subject to judicial notice." *Akhtar v. Mesa*, 698 F.3d 1202, 1212 (9th Cir. 2012); *see also United States v. Ritchie*, 342 F.3d 903, 908 (9th Cir. 2003) (finding that under the 12(b)(6) standard, "if a district court considers evidence outside the pleadings, it must normally convert the 12(b)(6) motion into a Rule 56 motion for summary judgment…."). A court "must take judicial notice if a party requests it and the court is supplied with the necessary information." Fed. R. Evid. 201(c). That is, the party requesting judicial notice must show that the fact "is not subject to reasonable dispute" because it is either generally known or "can be accurately and readily determined from sources whose accuracy cannot reasonably be questioned." *Lee v. City of Los Angeles*, 250 F.3d 668, 689 (9th Cir. 2001) (quotation omitted); Fed. R. Evid. 201(b).

Defendants ask the Court to take judicial notice of twenty-two exhibits comprised of documents from the FDA and scholarly articles. (Docket No. 24-1). Plaintiffs object on the basis that the documents are unauthenticated and inadmissible extrinsic evidence, which the Court should not consider at the pleadings stage. (Docket No. 31 at 5–6). Alternatively, Plaintiffs' request that the Court take judicial notice of twenty-two exhibits attached to Plaintiffs' Opposition. (*Id.* at n.6). Notably, a court may take judicial notice of the contents of an exhibit, without converting a

motion to dismiss into a motion for summary judgment based on the fact that the exhibit is publicly available. *See Galindo v. Ocwen Loan Servicing, LLC*, 282 F. Supp. 3d 1193, 1196 (N.D. Cal. 2017) ("Matters of public record are the appropriate subjects of judicial notice."); *see also Spy Optic, Inc. v. Alibaba.Com, Inc.*, 163 F. Supp. 3d 755, 763 (C.D. Cal. 2015) (finding that a court "may take judicial notice of the fact that an internet article is available to the public, but it may not take judicial notice of the truth of the matters asserted….").

Likewise, Plaintiffs also affixed twenty-two exhibits to their Opposition through the Declaration of Connor G. Sheehan ("Sheehan Decl.") and argued that if the Court disagrees and takes notice of Defendants' exhibits, then the Court should also take judicial notice of all of their exhibits. (Document 31 at 6, n.6). These exhibits include scientific literature about Libtayo and SJS/TEN, safety data referenced in the Complaint, and "evidence Defendants chose not to attach to their Motion." (*Id.*). As Defendants indicated, Plaintiffs did not file a separate motion seeking judicial notice or otherwise explain the basis for their application other than in a footnote in their Opposition. (*Id.*). The Court considers the exhibits by category.

A. FDA Documents

i. *Defendants' Exhibits A-M*

Defendants request that the Court take judicial notice of thirteen exhibits, which are documents publicly available on the FDA's website including Libtayo's license application and labeling approval letters for various drugs classified as PD-1/PDL-1 inhibitors such as Libtayo, Keytruda, Opdivo, and Tecentriq, an FDA multi-disciplinary review on Libtayo, and a printout from the FDA adverse events reporting system public dashboard. (Docket Nos. 24-3–15, Exhs. A–M). The Court finds that this category of documents is appropriate for judicial notice because they are publicly available on the FDA's website and therefore are "capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned." *Funke v. Sorin Grp. USA, Inc.*, 147 F. Supp. 3d 1017, 1025 (C.D. Cal. 2015); *see also*

Fed. R. Evid. 201(b). The Court, however, will only take judicial notice of the fact that these documents are available to the public, but will not take judicial notice of the truth of the matters asserted. *See Spy Optic*, 163 F. Supp. 3d at 763.

ii. *Plaintiffs' Exhibit B*

Notwithstanding Plaintiffs' failure to provide a basis for judicial notice of this document, the Court will take judicial notice of Exhibit B, which is a printout of the FDA's website as it can be "accurately and readily determined from sources whose accuracy cannot reasonably be questioned." Fed. R. Evid. 201(c). The Court will not take judicial notice of the truth of the matters asserted. *See Spy Optic*, 163 F. Supp. 3d at 763.

B. Scientific Articles

i. *Defendants Exhibits N-V*

Defendant also seeks judicial notice of nine exhibits, which are scholarly articles cited to in Plaintiffs' Complaint. (Docket Nos. 24-16–24, Exhs. N–V). Plaintiffs cite these nine exhibits throughout its Complaint to support their allegations that Defendants failed to disclose newly acquired safety information to the FDA. (Compl., Docket No. 1 ¶¶ 49–70). The Court will similarly also take judicial notice of these scholarly articles as they are incorporated by reference in the Complaint. *See e.g. In re Tesla, Inc. Sec. Litig.*, 477 F. Supp. 3d 903, 920 (N.D. Cal. 2020) (taking judicial notice of the public existence of various documents including scholarly articles because they were incorporated by reference in the operative complaint, but not considering the exhibits to the extent the articles contradict factual allegations). The Court, however, does not take judicial notice of the truth of the matters asserted to the extent that these articles contradict factual allegations pled in the Complaint. *Id.*

ii. *Plaintiffs' Exhibits C–V*

Similar to Defendants, Plaintiffs seek to admit scholarly articles, which are incorporated by reference in Plaintiffs' Complaint (Exhibits C–V). The Court will take judicial notice of these scholarly articles as they are incorporated in the

Complaint. *See In re Tesla*, 477 F. Supp. 3d at 920. The Court, however, will not take notice of the truth of the matters asserted, especially as to disputed facts, which is not proper at this juncture. *See id*.

IV. MOTION TO DISMISS

A. Label Adequacy

Defendants contend that all four of Plaintiffs' causes of action rely upon the common allegation that the Libtayo label failed to adequately warn physicians in plain and explicit terms of the dangers of SJS and TEN. (Docket No. 24 at 11). As such, Plaintiffs' entire Complaint may be dismissed as a matter of law if the Court finds that the Libtayo product label was adequate. Plaintiffs do not dispute this claim and simply argue the merits of the adequacy of Libtayo's label. The Court finds that causes of action for negligence, and strict products liability under a failure to warn theory share the same common allegation of the adequacy of the label and a finding that the label was adequate can dismiss the entire complaint. *See, e.g. Mahnke v. Bayer Corp*., No. 219CV07271RGKMAA, 2019 WL 8621437, at *2 (C.D. Cal. Dec. 10, 2019) (quoting *Carlin v. Superior Court*, 13 Cal. 4th 1104, 1112 (1996)) (A strict liability claim requires a showing that a manufacturer and/or distributor "failed to adequately warn of a particular risk that was known or knowable in light of the generally recognized and prevailing best scientific and medical knowledge available at the time of manufacture and distribution," whereas under a negligence cause of action liability exists if "a manufacturer or distributor did not warn of a particular risk for reasons which fell below the acceptable standard of care, i.e., what a reasonably prudent manufacturer would have known and warned about."). Thus, the Court will only address the adequacy of the label issue and not any of the other elements of each cause of action, which are not at issue in this Motion.

A drug manufacturer has a duty "to warn physicians about the risks known or reasonably known to the manufacturer." *T.H. v. Novartis Pharms. Corp*., 4 Cal. 5th 145, 164 (2017) (internal citation omitted). In California, a drug manufacturer's

responsibility to warn of the potential side effects of prescription drugs "runs to the *physician*, not to the patient." *Carlin*, 13 Cal. 4th at 1116 (emphasis in original) (explaining that under the learned intermediary doctrine applied in California, the duty to warn falls upon the physician, not the patient). Physicians typically rely on a prescription drug's warning label. *Novartis*, 4 Cal.5th at 178. "If adequate warning of potential dangers of a drug has been given to doctors, there is no duty by the drug manufacturer to insure [sic] that the warning reaches the doctor's patient for whom the drug is prescribed." *Stevens v. Parke, Davis & Co*, 9 Cal. 3d 51, 65 (1973). A warning is adequate if it "directly warns in plain and explicit terms of the specific risk that has caused injury to the plaintiff." *Patton v. Forest Lab'ys, LLC*, No. EDCV17922MWFDTBX, 2018 WL 5270476, at *14 (C.D. Cal. May 10, 2018), *aff'd sub nom*. *Patton v. Forest Lab'ys, Inc.*, 793 F. App'x 608 (9th Cir. 2020) (internal quotation marks and citations omitted). A claim for a failure to warn must include allegations that "identify which danger was not warned against, explain that the danger was substantial, and that the danger was known or reasonably knowable, or explain how any warning that was given was inadequate." *Marroquin v. Pfizer, Inc.*, 367 F. Supp. 3d 1152, 1160–61 (E.D. Cal. 2019). "Whether the warning is adequate is usually a question of fact." *Schwoerer v. Union Oil Co.*, 14 Cal.App.4th 103, 112 (1993).

Here, as mentioned above, *supra* I.B.i, Libtayo's 2021 label included two references to SJS and TEN. Specifically, in a section entitled "Warnings and Precautions: Severe and Fatal Immune-Mediated Adverse Reactions," the label states in part: "LIBTAYO can cause immune-mediated rash or dermatitis." (Docket No. 24-10; Exh. H at 9). The warning continues to state in part: "Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with PD-1/PD-L1 blocking antibodies." (Docket No. 24-10; Exh. H at 9). The warning then refers to a section entitled "Recommended Dosage Modifications for Adverse

Reactions," with instructions to either "withhold" dosages if a patient is suspected of SJS or TEN or "permanently discontinue" if SJS or TEN is confirmed. (*Id.* at 4).

Defendants contend this label has "*always* identified SJS/TEN as a risk in plain and explicit terms" and is adequate as a matter of law. (Docket No. 24 at 4) (emphasis in original). The Court disagrees. Plaintiffs have alleged sufficient facts, which if accepted as true, demonstrate that Libtayo's label failed to adequately warn physicians of the risks of SJS and TEN. Plaintiffs' Complaint lists six examples (referred to as the "Krantz Warnings") demonstrating the alleged inadequacies of the label. (Docket No. 1 ¶ 9). For example, one of the Krantz Warnings alleges that the above-mentioned warnings are inadequate because they do not mention anything about fatal cases in Libtayo's clinical trials due to SJS and TEN. (Docket No. 1 ¶¶ 9, 50–58). These allegations, taken as true, demonstrate that there are dangers that were not warned against (i.e., fatalities due to SJS and TEN), which were reasonably known to Defendants as they are supported by Libtayo's clinical data and in scholarly articles.. (*Id*.). At this juncture, these allegations sufficiently demonstrate that the label failed to adequately warn physicians of the fatal risk of SJS and TEN. *See e.g. Rosewolf v. Merck & Co*., 635 F. Supp. 3d 830, 839 (N.D. Cal. 2022) (holding that a cause of action for a failure to warn was sufficiently pled because it included "facts that describe the information available to Defendants about the risk of severe neuropsychotic events… as well as facts to show why [the drug manufacture's] label allegedly did not adequately warn of those dangers.").

Furthermore, the Complaint contains allegations from Dr. Vora that he was unaware of the risks of SJS and TEN from Libtayo, such as the higher risk to female patients like Mrs. Krantz, which was not apparent from the labeling. (*Id.* ¶ 11, 71–80). Defendants argue that Dr. Vora's allegations are self-serving and irrelevant to the issue of the adequacy of the labeling because whether Dr. Vora was aware of the risks

of SJS and TEN is a "factual question related to the issue of *proximate causation*…."[3] (Docket No. 24 at 13 n. 29). The Court finds this argument unpersuasive. The allegations surrounding Dr. Vora as to the warning he received and how it related to Mrs. Krantz, which must be accepted as true at the pleadings phase, are directly related to the adequacy of the label claim—not just proximate causation.[4] *See e.g. Fischer v. Bos. Sci. Corp*., No. SACV1902106JVSDFM, 2020 WL 2300138, at *3 (C.D. Cal. Mar. 25, 2020) (finding an allegation of failure to warn insufficiently pled because it *did not* include allegations about plaintiff's physician, "what warning the physician received, or how the warnings that were disclosed to the physician were inadequate."). Ultimately, Plaintiffs' allegations are sufficient to show that the label is inadequate and thus the adequacy of the warning label is a question of fact for the jury to decide. *Miles Labs., Inc. v. Superior Court*, 133 Cal. App. 3d 587, 184 Cal. Rptr. 98, 104 (1982) (when a "warning on a drug label is ambiguous… the adequacy of the warning becomes a question of fact for the jury."). Accordingly, the Court **DENIES** Defendants' Motion on the grounds of the adequacy of the labeling.

B. Preemption

Defendants contend that Plaintiffs' state law claims are preempted under the Supremacy Clause of the United States Constitution pursuant to the affirmative defense of impossibility preemption. (Docket No. 24 at 18–31). Impossibility

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[3] During oral arguments, Defendants cited *Quinn-White v. Novartis Pharms. Corp.*, No. CV164300PSGAGRX, 2018 WL 6133637, at *7 (C.D. Cal. Mar. 7, 2018) to support their argument that the Court's reliance on Dr. Vora's affidavit is improper at this stage because it is not subject to judicial notice. The Court, however, did not reference Dr. Vora's *affidavit*. Rather, the Court cites to the allegations included in the *Complaint* regarding Dr. Vora's lack of knowledge of the risk due to inadequate warnings. As stated above, an allegation in a complaint regarding a doctor's lack of knowledge is proper for the court to consider at this phase. In fact, at least one court—*Fischer*—dismissed an action in part for a complaint's failure to include any allegations from the treating physician about the warnings that they received.

[4] While it is true that some of Dr. Vora's claims—including his reliance on the labeling and whether he would have acted differently if he had been properly informed of those risks—may be relevant to proximate causation, such allegations do not negate the adequacy allegations.

preemption occurs when a conflict between federal and state law makes "compliance with both federal and state regulations [] a physical impossibility…." *Wyeth v. Levine*, 555 U.S. 555, 568 (2009). Notably, "[i]mpossibility pre-emption is a demanding defense." *Wyeth*, 555 U.S. at 573. "The question for impossibility is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011) (internal quotation marks omitted). This question of preemption is for the judge and not the jury. *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S.Ct. 1668 (2019). "[T]he judge must simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflic[t].'" *Id*. at 1679 (citations omitted).

Under the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301, *et seq*. drug manufacturers are required to submit a new drug application ("NDA"), including reports of investigations and specimens of proposed labeling to the FDA before any new drug could be marketed and sold to the public. 21 U.S.C. § 355(b). "[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" including "for the accuracy and adequacy of its label as long as the drug is on the market." *Wyeth*, 555 U.S. at 570–71. In general, the FDA must approve any subsequent label change through a supplemental application process. 21 C.F.R. § 314.70(b)(2)(v)(A). A manufacturer, however, may "unilaterally update a label, without waiting for FDA preapproval, 'to add or strengthen a contraindication, warning, precaution, or adverse reaction' under the 'changes being effected' ("CBE[]") regulation." *Novartis*, 4 Cal. 5th at 158 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). This unilateral label change under the CBE provision makes the change effective immediately while pending FDA review, "so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Albrecht*, 139 S.Ct. at 1679 (citing 21 C.F.R. § 314.70(c)(6)(iii)).

In the context of preemption by the FDCA of claims of failure-to-warn, the burden is first on the Plaintiffs to "allege facts showing that [defendant] could have unilaterally changed [the drugs'] label under the CBE regulation." *Mahnke v. Bayer Corp.*, No. 219CV07271RGKMAA, 2019 WL 8621437, at *3 (C.D. Cal. Dec. 10, 2019) (internal quotation marks and citation omitted). Once Plaintiffs have alleged such facts, then Defendants must demonstrate by "clear evidence that the FDA would not have approved the labeling change." *Id.* (internal quotation marks and citation omitted).

Defendants contend that Plaintiffs have not met their burden of alleging newly acquired evidence from post-FDA approval of Libtayo, which would allow Defendants to unilaterally change the label through the CBE process. Further, even if Plaintiffs have sufficiently alleged newly acquired evidence, their claims still fail because there is "clear evidence" that the FDA would not have approved the labeling change that Plaintiffs allege is necessary under the Krantz Warnings, because the FDA had already reviewed these changes and declined to adopt them. The Court will address each argument in turn.

i. *Newly Acquired Information*

In order to utilize the CBE process to unilaterally change a label, a drug manufacturer must show "newly acquired information" about the "evidence of a causal association" between the drug and a risk of harm. *Albrecht*, 139 S.Ct. at 1673 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). The FDA defines newly acquired information as:

> 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.

21 C.F.R. § 314.3(b).

The Supreme Court has further clarified that in this context, the "newly acquired information" is not limited to new data, but "also encompasses 'new analyses of previously submitted data.'" *Wyeth*, 555 U.S. at 571 (quoting 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008)). This is because "risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Id.*

Here, the Complaint cites the following as evidence of newly acquired information: (1) undisclosed cases of serious skin reactions from Libtayo's own clinical trials and from scholarly articles; (2) articles referencing the increased risk of SJS and TEN to subpopulations including females; (3) Libtayo's foreign labeling used in Canada, Australia, and the European Union, which contain stronger warnings for SJS and TEN; and (4) the FDA's adverse events public database for Libtayo.[5] (Docket No. 1 ¶¶ 50–65). The Court finds that Plaintiffs' allegations of newly acquired information, if accepted as true, are sufficient at the pleadings phase to satisfy their burden that Defendants could have unilaterally changed Libtayo's label under the CBE regulation. Among other things, the Complaint contained a scholarly article cited and incorporated by reference discussing immune-related adverse events associated with PD-1/PD-L1 class drugs (the "*Chen* article"). (Docket No. 1 ¶¶ 56–57; *see also Chen* article, Docket No. 31-5, Exh. C). The *Chen* article was published in 2021, after FDA approval of Libtayo, but before Mrs. Krantz was prescribed Libtayo, and used data from January 2004 to December 2019. (Docket No. 1 ¶ 56). Contrary to Defendants claims that the article did not test Libtayo or analyze SJS/TEN, the *Chen* article clearly states that among the PD-1 inhibitors, Libtayo (referred to in the article under its other name cemiplimab) had the highest rate of skin

[5] The parties dispute the universe of categories and types of evidence alleged in the Complaint that qualify as newly acquired evidence. The Court declines to opine as to each category or type of evidence since even finding one source of newly acquired information is sufficient to survive a motion to dismiss for impossibility preemption.

toxicities (encompassing 45 types, two of which were SJS and TEN) and fatalities of the PD-1 inhibitors and instructed further safety studies were necessary. (Docket No. 1 ¶¶ 57–58; *see also* Docket No. 31-5, Exh. C). These allegations are sufficient to find that Defendants could have unilaterally engaged in the CBE process "to add or strengthen a contraindication, warning, precaution, or adverse reaction." *Wyeth*, 555 U.S. at 569–71 (finding persuasive that as more cases of adverse reactions occurred, the manufacturer "could have analyzed the accumulating data and added a stronger warning" about the potential risks).

Defendants argue that the clinical trials and scholarly articles are insufficient because they either were previously submitted to the FDA prior to the approval of the 2018 label and before Mrs. Krantz received Libtayo and thus were not newly acquired information "not previously submitted to the Agency."[6] (Docket No. 24 at 20) (citing 21 C.F.R. § 314.3(b)). The Court disagrees as indicated by the above-mentioned discussion regarding the *Chen* article. Notably, the fact that some of the articles and studies cited by Plaintiffs may have been previously provided to the FDA or are outside of the relevant time period (i.e. after FDA approval in September 2018 but before Mrs. Krantz was prescribed Libtayo in April 2022) is not entirely preclusive. As the Supreme Court indicated in *Wyeth*, the limitation to "newly acquired information" does not necessarily mean that it must be new data. *Wyeth*, 555 U.S. at 571. Accordingly, the Court finds that Plaintiffs have met their burden to demonstrate that Defendants could have unilaterally engaged in the CBE process and therefore

[6] Note that Plaintiffs make a distinction between pre-approval or post-approval preemption claims. Because Defendants did not clearly address pre-approval preemption claims in its Motion and only raised them for the first time in their Reply, Plaintiff argues that Defendants waived any pre-approval preemption claims. The Court agrees that Defendants only addressed post-approval preemption claims (i.e. utilizing the CBE regulation) and thus will not address the pre-approval preemption issues. *See e.g. Holley v. Gilead Scis., Inc.*, 379 F. Supp. 3d 809, 826 (N.D. Cal. 2019) ("[T]he Court does not read *Levine* as requiring preemption of all failure-to-warn claims, including pre-approval claims, based on material that has been presented to the FDA.").

were not preempted on this ground.

ii. *Clear Evidence*

Next, the Court must determine if Defendants have demonstrated by "clear evidence" that the FDA would not have approved a change to the Libtayo label. A state law failure-to-warn claim is preempted by the FDCA "where there is 'clear evidence' that the FDA would not have approved the warning that state law requires." *Albrecht*, 139 S. Ct. at 1676, 1679 (citing *Wyeth*, 555 U.S. at 571) (stating that only "agency actions taken pursuant to the FDA's congressionally delegated authority" and "carrying the force of law" can constitute such clear evidence for preemption purposes). To determine if clear evidence exists, courts must look to whether "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." *In re Incretin-Based Therapies Prod. Liab. Litig.,* 524 F. Supp. 3d 1007, 1018 (S.D. Cal. 2021), aff'd, No. 21-55342, 2022 WL 898595 (9th Cir. Mar. 28, 2022) (citing *Albrecht*, 139 S. Ct. at 1672). "If the answer to the clear evidence question is yes, then the state law claim is preempted." *Id.*

Defendants argue that in 2020, before Mrs. Krantz was prescribed Libtayo, the FDA sought to "harmoniz[e]" the adverse effect warnings for all PD-1/PD-L1 drugs including SJS and TEN. (Docket No. 24 at 28–29). As a result, warnings from the label of another other PD-1/PD-L1 drug (Keytruda) removed a warning that SJS/TEN could be fatal and additional monitoring instructions for SJS/TEN. (*Id.*; *see also* Keytruda FDA Approved Label, Docket Nos. 24-6, 24-8, Exhs. D, F). Defendants argue that this encompasses two of the Krantz Warnings, and as such is clear evidence that the FDA would not have approved Plantiffs' Krantz Warnings. (*Id.* at 30–31). The Court finds this unpersuasive. Examples of how the FDA may communicate disapproval of a warning include: "(1) by means of notice-and-comment rulemaking setting forth labeling standards (2) by formally rejecting a warning label that would

have been adequate under state law, or (3) with other agency action carrying the force of law." *In re Incretin-Based Therapies Prod. Liab. Litig.,* 524 F. Supp. 3d at 1030 (citing *Albrecht*, 139 S. Ct. at 1679). In the present matter, the Krantz Warnings allege six separate missing warnings from the Libtayo label. Even assuming Defendants' argument is true, the FDA's change addressed only two of Plaintiffs' alleged inadequacies with the label. Moreover, it is unclear—based on the Complaint and FDA letters related to Keytruda—whether the FDA was fully informed of the justifications for all of the Krantz Warnings including for the other Krantz Warnings. Accordingly, at this juncture, Defendants have not met their burden of demonstrating "clear evidence" that the FDA would not have approved a change to the Libtayo label, and thus Defendants Motion as to impossibility preemption is **DENIED**.

V. CONCLUSION

For the reasons discussed above, the Court **GRANTS** Defendants' RJN, **GRANTS** Plaintiffs' request for judicial notice and **DENIES** Defendants' Motion. Defendants are **ORDERED** to file an answer within 14 days of the date of this Order.

IT IS SO ORDERED.

Dated: April 24, 2024

HON. WESLEY L. HSU
UNITED STATES DISTRICT JUDGE