UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION As to all related and member cases	Case No.: 13md2452 AJB (MDD) **ORDER GRANTING DEFENDANTS' MOTION FOR SUMMARY JUDGMENT AND DENYING PLAINTIFFS' CROSS-MOTION FOR SUMMARY JUDGMENT** (Doc. Nos. 1163, 1166)

I. INTRODUCTION

Through the enactment of the Federal Food, Drug, and Cosmetics Act, 21 U.S.C. § 301 *et seq.*, Congress delegated authority to the Food and Drug Administration ("FDA") to regulate pharmaceutical manufacturers and their products. With subsequent amendments, Congress enlarged this authority, charging the FDA with the power to protect the public health, and to assure the safety, effectiveness, and reliability of drugs. In discharging its regulatory duties, the FDA oversees the introduction of new drugs into the market, regulates the content of drug labeling, and ensures manufacturers comply with postmarketing requirements. Despite the FDA's broad regulatory duties, a drug manufacturer remains primarily responsible for maintaining the adequacy of product

labeling. State tort law is therefore generally viewed as a complimentary form of drug regulation, providing additional protections and recourse for injured consumers. Yet, when state tort law imposes a duty impossible to meet in light of FDA regulations, federal law will preempt state law. Impossibility preemption is a form of conflict preemption and is a demanding defense—requiring a drug manufacturer to establish by clear evidence that the FDA would reject a proposed labeling change.

Despite the high burden imposed on a preemption proponent, the unprecedented facts of this case cross the clear evidence threshold, making Defendants' preemption defense not only viable, but also dispositive of Plaintiffs' failure-to-warn claims. The record establishes the FDA has specifically considered pancreatic cancer risk, commented publicly on the adequacy of drug labeling, and maintained its position that scientific evidence of a causal association between incretin mimetics and pancreatic cancer is indeterminate. Because an indeterminate causal association falls below the federal regulatory standards required for labeling changes, clear evidence exists that the FDA would have rejected a reference to pancreatic cancer in product labeling. For the reasons set forth below, the Court **GRANTS** Defendants' motion for summary judgment and **DENIES** Plaintiffs' cross-motion for summary judgment on the affirmative defense of conflict preemption.

II. BACKGROUND

This multidistrict litigation involves claims that Defendants failed to warn that four prescription drugs used to treat type 2 diabetes cause or create an increased risk of pancreatic cancer. Plaintiffs are individuals with type 2 diabetes who were prescribed and consumed one or more of the prescription drugs marketed respectively as Januvia, Janumet, Byetta, and Victoza.[1] Defendants are the pharmaceutical companies that

[1] The drugs are sometimes referred to by their active ingredients. Sitagliptin is the active ingredient in Januvia and Janumet, exenatide is the active ingredient in Byetta, and liraglutide is the active ingredient in Victoza.

manufacture and market the drugs, including Amylin Pharmaceuticals, LLC ("Amylin"), Eli Lilly and Company ("Lilly"), Merck Sharp & Dohme Corp. ("Merck"), and Novo Nordisk Inc. ("Novo") (referred to collectively as "Defendants").

Byetta obtained FDA approval in April 2005. (Doc. Nos. 202-1 ¶ 38; 1163-2 Ex. F.) The FDA approved Januvia in October 2006 and Janumet in March 2007. (Doc. Nos. 202-1 ¶¶ 34, 36; 1163-2 Exs. G, H.) Victoza obtained FDA approval in January 2010. (Doc. Nos. 1163-1 at 8; 1163-2 Ex. I.) Byetta and Victoza are glucagon-like peptide-1 (GLP-1) receptor agonists, and Januvia and Janumet are dipeptidyl peptidase-4 (DPP-4) inhibitors. (*Id.* ¶ 33.) Although GLP-1 receptor agonists and DPP-4 inhibitors are different classes of drugs, for the purposes of this litigation the parties treat them the same. (*See generally* Doc. Nos. 206, 1163, 1166.) The FDA has also reviewed both classes of therapeutic agents as a whole, recognizing all four drugs under the broader terms of incretin mimetics or incretin-based therapies. (*See* Doc. Nos. 202 ¶ 33; 1163-3 at 3; 1166-10 at 2.)

Plaintiffs allege Defendants should have referenced pancreatic cancer in their product labeling.[2] Defendants assert Plaintiffs' failure-to-warn claims are conflict preempted because it would be impossible to reference pancreatic cancer in the drug labeling and comply with FDA labeling regulations. Defendants initially moved for summary judgment premised on conflict preemption in April 2014. (Doc. No. 410.) The Court denied the motion without prejudice and granted Plaintiffs' request for additional discovery pursuant to Federal Rule of Civil Procedure 56(d). (Doc. No. 472.) In June 2015, following discovery focused on conflict preemption, Defendants renewed their motion for summary judgment, (Doc. No. 1163), and Plaintiffs filed a cross-motion for

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[2] Plaintiffs argue Defendants should have warned about an increased risk of pancreatic cancer or listed pancreatic cancer as a possible adverse reaction associated with the use of the drugs. Any mention by the Court of a pancreatic cancer "reference" in the product labeling encompasses either a warning about pancreatic cancer or listing pancreatic cancer as an adverse reaction.

summary judgment, (Doc. No. 1166). The Court heard oral argument on the motions on September 11, 2015. (*See* Doc. No. 1445.)[3]

III. LEGAL STANDARD

Federal Rule of Civil Procedure 56 governs motions for summary judgment. Summary judgment permits a court to enter judgment on factually unsupported claims, *see Celotex Corp. v. Catrett*, 477 U.S. 319, 327 (1986), and may also be used in the area of affirmative defenses. *Dam v. Gen'l. Elec. Co.*, 265 F.2d 612, 614 (9th Cir. 1958). Granting summary judgment is proper if there is "no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A fact is material when, under the governing substantive law, it could affect the outcome of the case. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). A dispute about a material fact is genuine "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Id.* Where parties file cross-motions for summary judgment, a court must consider each party's evidence, regardless of which motion offers the evidence. *Tulalip Tribes of Wash. v. Washington*, 783 F.3d 1151, 1156 (9th Cir. 2015); *Las Vegas Sands, LLC v. Nehme*, 632 F.3d 526, 532 (9th Cir. 2011).

IV. DISCUSSION

Under the Supremacy Clause, "Congress has the power to preempt state law." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000); *see also Oneok, Inc. v. Learjet, Inc.*, 135 S. Ct. 1591, 1594–95 (2015). A preemption analysis begins with two

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[3] Pursuant to the agreement of all parties, the Court held joint oral argument with the pancreatic cancer cases pending in the Los Angeles County Superior Court (Case No. JCCP 4272), in an effort to promote the convenient and efficient resolution of nearly identical preemption-based motions for summary judgment pending in the state and federal proceedings. *See In re Phenylpropanolamine (PPA) Products Liab. Litig.*, 460 F.3d 1217, 1222 (9th Cir. 2006) (noting a court's statutory charge in a multidistrict litigation proceeding is to promote the just and efficient conduct of the actions pursuant to 28 U.S.C. § 1407). While the hearing was held jointly, the Court has deliberated individually without any discussion of the merits of the parties' claims, including the applicable law or the facts, with the judge presiding over the JCCP proceedings.

governing principles. First, Congressional intent is the "ultimate touchstone." *Wyeth v. Levine*, 555 U.S. 555, 565 (2009). Second, in a field the States have traditionally occupied, there is a presumption against preemption based on the notion that "Congress does not cavalierly pre-empt state-law causes of action." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996).

Preemption occurs in three forms: (1) express preemption; (2) field preemption; and (3) conflict preemption. *Ting v. AT&T*, 319 F.3d 1126, 1135 (9th Cir. 2003). Express preemption exists "where Congress enacts an explicit statutory command that state law be displaced." *Id.* Field and conflict preemption are forms of implied preemption. Field preemption occurs when federal regulation is sufficiently comprehensive that it leaves no room for supplementary state regulation. *Hillsborough Cnty., Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712–13 (1985). Conflict preemption occurs when: (1) "compliance with both federal and state regulations is a physical impossibility," or (2) "state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.* (internal citation and quotation marks omitted).

Plaintiffs' claims are not expressly preempted by federal statute, and prescription drug regulation is a field in which the States have traditionally occupied. *See Reigel v. Medtronic, Inc.*, 552 U.S. 312, 327 (2008) (noting Congress could have expressly preempted claims regarding pharmaceutical drugs, but chose not to); *Lefaivre v. K.M. Pharm., Inc.*, 636 F.3d 935, 941 (8th Cir. 2011)(citing *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–67 (1989)("[T]he FDA [has] long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.")). Defendants do not assert Plaintiffs' claims create an obstacle to the full purposes and objectives of Congress, and thus obstacle preemption is not at issue. As such, the Court's inquiry will focus on whether concurrent compliance with federal regulations and state tort law is impossible.

As an initial matter, at oral argument Plaintiffs challenged whether conflict preemption presents an issue of law or an issue of fact, and whether resolution by

summary judgment is appropriate. (*See, e.g.*, Doc. No. 1445 at 64–65, 127:3–22.) Following oral argument, the state court requested additional briefing specific to this issue. (*See* Doc. No. 1502 at 1.) At the agreement of the parties in this case, that briefing was submitted as supplemental authority in these proceedings. (*Id.*) Upon consideration of the arguments presented in the supplemental briefing, relevant authority, and the pending cross-motions for summary judgment, the Court is satisfied that preemption presents purely a question of law appropriate for resolution by summary judgment. *See Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1267 (W.D. Okla. 2011) ("Where, as here, the moving party asserts entitlement to judgment because a claim is preempted by federal law, the motion presents only a legal question for the court; if the court concludes that a state law claim is preempted, summary judgment is proper as to that claim."); *see also Bank of Am. v. City & Cnty. of San Francisco*, 309 F.3d 551, 566 (9th Cir. 2002) (affirming the district court's grant of summary judgment based on federal conflict preemption). Moreover, Plaintiffs' affirmative motion for summary judgment in these proceedings supports the Court's conclusion that summary judgment is appropriate for resolution of Defendants' conflict preemption defense.

A. Relevant law

In the context of pharmaceutical drug regulation and state law failure-to-warn claims, the Court is guided by the United States Supreme Court case of *Wyeth v. Levine*, which provides the standard Defendants must prove to establish impossibility preemption. The plaintiff in *Levine* received an injection of the drug Phenergan through the IV push method of administration. *Levine*, 555 U.S. at 559. When the drug was administered, it entered Levine's artery. *Id.* This caused gangrene and eventually required amputation of her right forearm. *Id.* Levine sued Wyeth, the manufacturer of Phenergan, arguing the drug's labeling was inadequate because it did not warn that medical professionals should use the IV drip method of administration instead of the IV push method. *Id.* at 560. Wyeth argued Levine's claims were preempted because it was impossible to comply with state law and the FDA's labeling requirements. *Id.*

Specifically, Wyeth argued it could not unilaterally change Phenergan's labeling to warn about dangers associated with the IV push method, and only "newly acquired information" implicated the Changes Being Effected ("CBE") regulation.[4] *Id.* at 568–69.

In analyzing Wyeth's conflict preemption defense, the Court concluded that initial FDA approval of drug labeling does not preempt a subsequent failure-to-warn claim. *Id.* at 558. Thus, the Court looked beyond initial drug approval and considered several factors as part of its preemption analysis, including: (1) whether Wyeth tried to give the warning sought by Levine and (2) whether it had been precluded from doing so; (3) whether the FDA or the manufacturer focused on the risks associated with IV push versus IV drip administration of Phenergan; and (4) whether Wyeth provided the FDA with an analysis or evaluation of those risks. *Id.* at 572–73. The evidence in *Levine* established Wyeth had not attempted to give a warning specific to IV push administration, and the FDA had not prohibited Wyeth from doing so. *Id.* Additionally, the evidence demonstrated the FDA and Wyeth had given only "passing attention" to the issue raised by Levine's claim. *Id.* at 572. There was also no evidence that Wyeth provided the FDA with an evaluation of the risks associated with the IV push method of administration. *Id.* at 572–73. Accordingly, the Supreme Court rejected Wyeth's preemption defense, concluding it was not impossible for Wyeth to provide the warning Levine sought. *Id.* at 573.

The Court then held that "absent clear evidence that the FDA would not have approved a change to Phenergan's label" the Court would "not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.* at 571. *Levine* therefore provides the relevant conflict preemption standard, but does not define what constitutes clear evidence. As such, application of the standard is necessarily fact-

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[4] Through submission of a CBE supplement, a manufacturer may make immediate changes to product labeling without requiring FDA approval of the change prior to product distribution. (*See, e.g.*, Doc. No. 1166-8 at 10 n.9); 21 C.F.R. § 314.70(c)(6).

specific.[5] *See Koho v. Forest Labs., Inc.*, 17 F. Supp. 3d 1109, 1118 (W.D. Wash. 2014) ("[T]he clear evidence standard is a fact based inquiry that depends on the express type of warning at issue and the particular facts of each case."); *Dobbs*, 797 F. Supp. 2d at 1270 (explaining that ascertaining conflict preemption is "necessarily fact specific").

The Ninth Circuit addressed conflict preemption in *Gaeta v. Perrigo Pharmaceuticals*,[6] with an analysis similar to that in *Levine*. *Gaeta* involved the generic manufacturer of ibuprofen, Perrigo, and a state law failure-to-warn claim regarding concurrent use of ibuprofen and other drugs known to cause liver toxicity. *Id.* at 1228. Perrigo asserted the plaintiffs' claims were conflict preempted. *Id.*

In support of preemption, Perrigo presented evidence that the FDA considered the general safety of ibuprofen on two separate occasions: once in 2002 in response to a citizen petition and a second time in 2006, when considering what types of warnings should be included in over-the-counter drugs, including ibuprofen. *Id.* at 1236–37. The Ninth Circuit held the FDA's general reviews of ibuprofen safety did not amount to clear evidence the FDA would not have approved the warnings suggested by the plaintiffs. *Id.* at 1237. The *Gaeta* court cited the lack of evidence that the FDA was presented with and actually considered the specific warning requested by the Gaetas. *Id.* The court also noted Perrigo did not suggest it supplied the FDA with an evaluation or analysis concerning concomitant use of ibuprofen and other drugs, and that the FDA refused to act. *Id.* (quoting *Levine*, 555 U.S. at 572–73). Finding the evidence presented was no more

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[5] The determination that conflict preemption is a fact-intensive analysis is consistent with the conclusion that it presents only a question of law suitable for determination by the Court through summary judgment. The factual inquiry is limited to what the FDA has done, if anything, in addressing the need for a warning on a particular drug. This is in contrast to considering the specific data relied upon by the FDA. *See infra* § F.

[6] 630 F.3d 1225 (9th Cir. 2011) *cert. granted, judgment vacated sub nom. L. Perrigo Co. v. Gaeta*, 132 S. Ct. 497 (2011). The Ninth Circuit's discussion of conflict preemption related to generic drug manufacturers was vacated following the Supreme Court's decision in *Pliva v. Mensing*, 131 S. Ct. 2567 (2011). *Pliva* is inapplicable in this matter because none of Defendants manufacture generic versions of the drugs at issue.

compelling than in *Levine*, the court concluded the Gaeta's claims were not preempted. *Id.*

As binding authority, *Levine* and *Gaeta* principally guide the Court's analysis. Notably, however, they both represent instances where the clear evidence standard is unsatisfied. At the opposite end of the spectrum are cases finding in favor of preemption. One such case, *Dobbs v. Wyeth Pharmaceuticals*, involved the use of selective serotonin reuptake inhibitors ("SSRI"), a class of antidepressants, and an increased risk of suicide. 797 F. Supp. 2d at 1266. Although characterized as an outlier by Plaintiffs, *Dobbs* demonstrates facts that meet the clear evidence standard and is useful in framing the continuum of conflict preemption case law.

In *Dobbs*, the plaintiff's husband committed suicide after taking the prescription drug Effexor as treatment for depression. *Id.* At the time of the suicide, Effexor's labeling and package insert included an FDA-approved statement regarding suicidality in adult patients diagnosed with depression. *Id.* The plaintiff argued the statement was inadequate to warn her husband of suicide risk. *Id.* The record in *Dobbs*, however, reflected extensive consideration by the FDA of an enhanced suicidality warning for adult patients, and the FDA's consistent conclusion there was "no scientific evidence of a causal association between SSRI's and increased suicidality warranting an enhanced warning." *Id.* at 1272–73. The evidence also established that following Effexor's initial approval, the FDA rejected citizen petitions asking for enhanced suicide warnings for Prozac, a different antidepressant, but within the SSRI class of drugs. *Id.* at 1274. In rejecting each citizen petition, the FDA cited insufficient evidence of an association between the SSRI and suicide risk. *Id.* Wyeth also demonstrated the FDA's position regarding an increased risk of suicide in adults did not change before or after the decedent's suicide. *Id.* Relying on the FDA's opinions that an enhanced suicidality warning was unsupported by

scientific data and the consistency of that opinion, the court concluded the plaintiff's claims were conflict preempted. *Id.* at 1277.[7]

A more recent case, *Rheinfrank v. Abbott Laboratories, Inc.*, No. 1:13cv114, 2015 WL 4743056 (S.D. Ohio, Aug. 10, 2015), also found the clear evidence standard satisfied. The plaintiff in *Rheinfrank* sued the manufacturer of an anti-epileptic drug taken during her pregnancy that resulted in developmental delay and other physical and cognitive injuries to her child. *Id.* at *2. In support of preemption, the manufacturer argued it sought FDA approval to add a developmental delay warning in the years after the plaintiff took the drug, but that the FDA concluded the scientific evidence was insufficient to support a warning. *Id.* at *6. The court concluded the FDA's consideration of the safety issue, and its failure to issue a labeling change in the years following the plaintiff's injury, constituted clear evidence the FDA would have rejected a label change at the time the plaintiff consumed the drug. *Id.* at *10.

Similarly, in *Reckis v. Johnson & Johnson*, 471 Mass. 272 (2015),[8] the court found the plaintiffs' claims partially preempted in light of the FDA's rejection of a warning sought by the plaintiffs. The plaintiffs' daughter suffered from Stevens-Johnson syndrome ("SJS") and toxic epidermal necrolysis ("TEN") after consuming Children's Motrin. *Id.* at 275. At the time the child took Motrin, the warnings section of the FDA-approved label contained an allergy alert warning that ibuprofen could cause an allergic reaction, but did not specifically reference SJS or TEN. *Id.* at 279. The manufacturer argued the plaintiffs' claims were conflict preempted. *Id.* at 281.

The record established that in the years after the incident, the FDA received a citizen petition concerning the relationship between ibuprofen and SJS and TEN. *Id.* at

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[7] Though *Dobbs* found cases regarding other drugs unpersuasive in its preemption analysis, the Court necessarily looks to cases regarding different pharmaceutical products in framing its analysis, and notes the parties take the same approach throughout their briefing.

[8] *petition for cert. docketed*, 15-449 (U.S. Oct. 9, 2015).

280. Following receipt of the petition, the FDA engaged in a "comprehensive review of the risks and benefits of ibuprofen, including the risks of SJS and TEN[.]" *Id.* (internal citation and quotation marks omitted). In the FDA's formal response to the citizen petition, the FDA agreed with the petitioners that labeling should be improved, but declined to include the specific terms SJS and TEN, concluding consumers were unfamiliar with those terms. *Id.* Relying on the citizen petition rejection, the court concluded the plaintiffs' claims specific to a warning regarding SJS and TEN were preempted, but claims related to a more general warning were not preempted. *Id.* at 290; *see also Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010) (noting "[t]he 'clear evidence' in this case is the agency's refusal to require a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do in a submission to which the agency was responding").[9]

In re Fosamax Products Liability Litigation, 951 F. Supp. 2d 695 (D.N.J. 2013), also presents an example of where a manufacturer established conflict preemption. In that case, the plaintiff was prescribed the drug Fosamax for the treatment of osteoporosis. *Id.* at 697. After taking the drug for several years, the plaintiff suffered a fracture in her right femur. *Id.* The plaintiff then filed suit against the manufacturer alleging it failed to adequately warn of risks associated with the use of Fosamax. *Id.* at 700. The manufacturer argued the plaintiff's claims were preempted because the FDA rejected a prior approval supplement ("PAS")[10] from the manufacturer that warned of femur fracture risk after the plaintiff's injury. *Id.* at 701, 703. The court agreed, concluding the FDA would not have approved a change to the Fosamax label prior to the plaintiff's

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[9] Defendants cited *Rheinfrank*, *Reckis*, and *Robinson* for the first time at oral argument. As recent decisions finding clear evidence the FDA would reject a proposed labeling change, the decisions are helpful to the Court's analysis to the extent they establish a lower threshold for a finding of preemption than that proposed by Plaintiffs.

[10] A manufacturer may utilize a PAS to propose changes that require FDA approval prior to distribution of the product with those changes. (*See* 21 C.F.R. § 314.70(b); Doc. No. 1166-8 at 10 n.9.)

injury given the FDA's rejection of the PAS with an enhanced warning only one month after the plaintiff's injury. *Id.* at 703. Finding the FDA's rejection constituted clear evidence under *Levine*, the court concluded plaintiff's claims were conflict preempted. *Id.*

Another case instructive to this Court's analysis is the Seventh Circuit's decision in *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387 (7th Cir. 2010), where the court concluded citizen petition rejections did not constitute clear evidence the FDA would reject a proposed warning. *Mason* involved the SSRI Paxil, and allegations the manufacturer failed to warn the drug caused an increased risk of suicide, particularly in young adults. *Id.* at 389. Citing the temporal gap between citizen petition rejections and the decedent's suicide, as well as the FDA's evolving opinion regarding pediatric suicidality, the court found it unlikely the FDA would have prevented the manufacturer from warning about suicide risk in young adults. *Id.* at 395 (noting the latest of the FDA's opinions regarding suicidality occurred several years before the decedent's suicide); *see also Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948 (E.D. Wis. 2009) (rejecting similar arguments as those advanced in *Mason* regarding the SSRI Prozac and distinguished by the court in *Dobbs*).

In *Dorsett v. Sandoz*, another SSRI case, the court similarly declined to rely on citizen petition rejections several years prior to the decedent's suicide as establishing preemption. 699 F. Supp. 2d 1142 (C.D. Cal. 2010). Dorsett involved a twenty-six year old man who committed suicide after taking a generic for the prescription drug Prozac. *Id.* at 1145. The manufacturer cited the FDA's rejection of a citizen petition requesting an enhanced warning as clear evidence the FDA would have rejected a label change. *Id.* at 1157. The court concluded the FDA's rejection of citizen petitions in the 1990s did not establish what the FDA would have done in response to a label change request in 2004. *Id.* The court also cited developments in scientific knowledge regarding SSRIs and suicidality leading up to the time of the suicide as weighing against preemption. *Id.* at 1157–58. Thus, the court concluded clear evidence did not exist that the FDA would have rejected an enhanced warning at the time of the suicide. *Id.* at 1158.

In *Koho v. Forest Laboratories, Inc.*, the court reached a similar conclusion. 17 F. Supp. 3d at 1109. In *Koho*, the plaintiff argued the manufacturer of the antidepressant Celexa should have included a warning about an increase in suicidal thoughts and emphasized the importance of communicating that risk to family members through product labeling. *Id.* at 1116–17. The manufacturer argued the plaintiff's claims were preempted and cited the FDA's rejection of three citizen petitions seeking an enhanced suicidality warning as support. *Id.* at 1117. The court found the FDA's rejection of citizen petitions unpersuasive, noting the most recent rejection, which occurred five years prior to the decedent's suicide, did not constitute clear evidence of what the FDA would have done at the time the decedent was prescribed Celexa. *Id.* The court also cited to subsequently implemented labeling that provided a warning similar to that sought by the plaintiff as weighing against preemption. *Id.* at 1119. Additionally, the court considered the similarities between the warnings rejected by the FDA in the citizen petitions and the warning sought by the plaintiff. *Id.* at 1116-17. Concluding the warnings were different—the plaintiff seeking a warning directed at family members of those taking the drug as opposed to a warning directed at the patient—the court found the plaintiff's claims were not conflict preempted. *Id.* at 1119.

Although the clear evidence standard remains undefined, these cases provide a framework from which the Court can apply *Levine* and its progeny to the facts in this matter. With *Levine* and *Gaeta* as examples of what is insufficient to warrant conflict preemption and *Dobbs* demonstrative of facts sufficient to establish the demanding defense, the Court must determine how the facts of this matter compare. Before doing so, however, the Court considers the federal regulatory construct within which Plaintiffs' claims arise.

B. Overview of federal drug regulation

Initial FDA approval of a drug is predicated, in part, on a manufacturer's use of FDA approved product labeling and package inserts. *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b). Following approval, the FDA can require postmarketing studies and drug

surveillance, and manufacturers have an ongoing duty to report the results of studies and drug surveillance to the FDA. 21 U.S.C. § 355(k)(1); 21 C.F.R. §§ 314.80, 314.81; *Dobbs*, 797 F. Supp. 2d at 1270 ("After a drug is approved by the FDA, manufacturers are required to maintain records, conduct additional testing as directed, and report to the FDA any significant adverse health consequences reported during the prescription drug's use."). The FDA is also responsible for continually monitoring the safety of approved drugs and may take action including withdrawal of approval if scientific data indicates a drug is unsafe. *See* 21 U.S.C. § 355(e).

Despite the FDA's ongoing regulatory role, drug manufacturers must maintain adequate product labeling in light of post-approval drug surveillance. *Levine* emphasized that a manufacturer bears the burden of maintaining the adequacy of product labeling at all times. *Levine*, 555 U.S. at 571 (noting manufacturers are charged with "crafting an adequate label and [] ensuring that its warnings remain adequate as long as the drug is on the market"). The CBE regulation permits manufacturers to reconcile this duty with the FDA's required approval of drug labeling by permitting a manufacturer to make immediate changes to product labeling without requiring FDA approval of the change prior to product distribution. (*See e.g.*, Doc. No. 1166-8 at 10 n.9); 21 C.F.R. § 314.70(c)(6). A manufacturer may submit a CBE based on "newly acquired information," which "encompasses new analyses of previously submitted data." *Levine*, 555 U.S. at 569.

A warning must be supported by "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6). A variety of sources can satisfy this standard, including adverse event rate,[11] evidence of a dose-response relationship, and the temporal association

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[11] FDA Guidance for Industry defines an adverse event as "any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related." (Doc. No. 1166-77 at 17); *see also* 21 C.F.R. § 314.80(a). Reports of adverse events, also referred to as spontaneous reporting, can be made even if the reporter is not certain that a product caused the medical event. (*See* Doc. No. 597 at 9) (citing FDA Adverse Event

between drug administration and the event. (Doc. No. 1166-11 at 6.) Federal regulations do not require that a causal association between a drug and a particular outcome be definitely established before it is added to product labeling as a warning. *See* 21 C.F.R. § 201.57(c)(i). A manufacturer is required to update its labeling as soon as reasonable evidence of a causal association exists. *Id.* §201.80(e). To include an adverse reaction in product labeling, federal regulations require there be some basis to believe there is a causal association. *Id.* § 201.57(c)(7).

The FDA also has the authority to mandate a labeling change if it learns of new safety information that it thinks should be included in the labeling of a drug. *See* 21 U.S.C. § 355(o)(4)(a). Similarly, the FDA can reject a CBE and require a manufacturer to remove the newly added language from its labeling. *See Levine*, 555 U.S. at 571. Unapproved labeling could be considered misbranded and subject to an FDA enforcement action. In practice, however, manufacturers often consult with the FDA about labeling issues prior to and after submission of a CBE, making an FDA enforcement action improbable. *Id.* at 570 ("[T]he very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept.").

Against this regulatory backdrop, the Court turns to the arguments and evidence offered by the instant cross-motions for summary judgment.

C. Clear evidence exists that the FDA would have rejected a pancreatic cancer reference in the product labeling

The parties raise several arguments both for and against preemption. Defendants assert they have established it would be impossible to comply with federal labeling requirements and state tort law, given the FDA's opinions regarding a causal association

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Reporting System (FAERS) http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm (last updated Sept. 10, 2012)).

between the drugs and pancreatic cancer. As support for this argument, Defendants cite seven instances where the FDA has taken a position regarding pancreatic safety: (1) issuance of the FDA's February 2014 assessment of pancreatic safety in the *New England Journal of Medicine*; (2) the FDA's rejection of a citizen petition requesting the withdrawal of Victoza; (3) the FDA's September 2014 conclusion that a causal association between incretin mimetics and pancreatic cancer is indeterminate; and (4)–(7) the subsequent approval of other incretin-based therapies without any reference to pancreatic cancer in the product labeling. (*See* Doc. No. 1445 at 9:21–25.) According to Defendants, each instance represents the FDA's opinion regarding pancreatic safety and its conclusion that current data does not support a pancreatic cancer reference.

Plaintiffs argue that absent actual and express rejection of a pancreatic cancer reference by the FDA, Defendants cannot establish clear evidence. Plaintiffs also contend that Defendants are aware of scientific evidence that satisfies the regulatory standards for inclusion of pancreatic cancer as a warning or adverse reaction. Though Defendants have not submitted a CBE or PAS, the evidence establishes the FDA has been aware of a pancreatic cancer safety signal[12] for several years, and actively investigated the existence of a causal relationship between the drugs and pancreatic cancer. (*See* Doc. No. 1163-3 at 73–74) (acknowledging the FDA has evaluated a pancreatic cancer safety signal for several years).

In 2009, the FDA reviewed its adverse event reporting system database for incidences of pancreatic cancer associated with Byetta, Januvia, and other antidiabetic therapies. (Doc. No. 1163-4 at 68–70.) After reviewing the database, the FDA concluded that "little inference for risk" could be appreciated from reviewing spontaneous reports of

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[12] FDA Guidance for Industry defines a safety signal as "a concern about an excess of adverse events compared to what would be expected to be associated with a product's use," which can arise from "postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class." (Doc. No. 554-9 at 8.)

pancreatic cancer, and that a causal association between the drugs and pancreatic cancer was indeterminate. (*Id.* at 80.) Based on that conclusion, the FDA did not make any labeling recommendations with respect to Byetta or Januvia. (*Id.*)

In April 2012, the FDA again considered pancreatic cancer risk in evaluating a citizen petition that called for the FDA to withdraw Victoza from the market. (Doc. No. 1163-3 at 25–52.) The petition cited adverse event data as demonstrative of an increased risk of pancreatic cancer. (*Id.* at 50.) Before responding to the citizen petition, the FDA issued a drug safety communication in March 2013 that directly related to pancreatic cancer risk associated with incretin mimetics. (Doc. No. 1163-4 at 85.) In the communication, the FDA stated it was "investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes." (*Id.*) The communication indicated the FDA would "obtain and evaluate" the new information and "communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report." (*Id.*) The FDA concluded the communication by stating it had not reached a new conclusion regarding pancreatic cancer risk, and advised health care professionals to continue following the prescribing recommendations in the drug labeling. (*Id.*)

As part of its review of incretin mimetics and pancreatic cancer risk, the FDA participated in the National Institute of Diabetes and Digestive Kidney Diseases and National Cancer Institute's workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013. (*Id.* at 88–94.) At the workshop, the FDA again acknowledged that adverse event data was "less suitable for detecting relatively more common events with long latency periods" such as pancreatic cancer. (Doc. No. 1163-4 at 90.) An FDA supervisory toxicologist at the workshop commented that incretin-based drugs were not associated with "overt pancreatic toxicity or pancreatic neoplasms . . . that would indicate a risk to human safety." (*Id.* at 89.) Moreover, the FDA acknowledged that sponsors of exenatide (Byetta), liraglutide (Victoza), and sitagliptin (Januvia and Janumet) completed

postmarketing pancreatic toxicology studies, which did not "definitively demonstrate[] a treatment-related adverse effect on exocrine histology or proliferation." (*Id.*)

Then, in February 2014, the FDA published its assessment of pancreatic safety in the *New England Journal of Medicine*. (Doc. No. 1163-3 at 4.) The article, titled "Pancreatic Safety of Incretin Mimetics–FDA and EMA Assessment" ("Assessment"), was authored by four FDA officials and members of the European Medicines Agency. (Doc. No. 1163 at 3.) As part of the Assessment, the FDA engaged in a comprehensive review of data including completion and review of its own pancreatic toxicity studies. (*Id.*) The FDA also reviewed clinical safety databases and the results of cardiovascular outcome trials in patients with type 2 diabetes who were treated with incretin-based drugs. (*Id.*) The Assessment directly addressed the relevance of pancreatic cancer adverse event reports, noting "inherent limitations to the ability to establish causal relationships" due to the high background rate and long latency period of pancreatic cancer.[13] (*Id.* at 2.) In conclusion, the FDA stated, "assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data." (*Id.*) The FDA also concluded the "current knowledge is adequately reflected in the product information or labeling" which did not warn of pancreatic cancer or list pancreatic cancer as an adverse reaction. (*Id.*)[14]

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[13] The FDA has recognized that adverse event reports have limited value in assessing a causal relationship because the National Cancer Institute does not characterize pancreatic cancer as a "rare" cancer, it has a long latency period, and shares risk factors recognized in patients with type 2 diabetes. (*See* Doc. No. 1163-4 at 73–74.) The National Cancer Institute characterizes a cancer as "rare" if there are fewer than 35,000 total cases per year. (*Id.* at 73.) The National Cancer Institute defines latency period as the time that passes between being exposed to something that can cause disease and having symptoms.

[14] The Assessment was updated with non-substantive information on June 5, 2014. (Doc. No. 1163-4 at 96.)

In March 2014, the FDA formally responded to the 2012 Victoza citizen petition. (Doc. No. 1163-3 at 25–61.) In doing so, the FDA rejected adverse event data as evidence of a causal association between Victoza and pancreatic cancer. (*Id.* at 50.) ("In our review of 49 unique cases recovered from [FDA Adverse Event Reporting System] we found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling."). The FDA also stated "[a]ny causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time." (*Id.*) Based on these conclusions, the FDA made no labeling recommendations specific to pancreatic cancer.

In September 2014, the FDA again reviewed pancreatic safety concerns in considering the safety of a higher dose of Victoza, marketed for weight loss as Saxenda. As part of a briefing document, the FDA acknowledged that pancreatic cancer had been "hypothesized but not proven" as a risk associated with incretin mimetics, and that "animal observations and clinical trial data reviewed by the FDA to date have not supported a causal association." (Doc. No. 1163-3 at 66.) The FDA also reiterated its earlier conclusion that studies were "inconclusive" as to a causal association between incretin mimetics and pancreatic cancer. (*Id.*) More recently, the FDA has reviewed pancreatic safety in connection with the approval of other incretin-based therapies not at issue in this litigation. None of the newly approved drugs reference pancreatic cancer in the product labeling. (*See, e.g.*, Doc. No. 1163-4 at 30, 35, 49, 64 Exs. N, O, P, Q.)

These facts establish the FDA has considered pancreatic cancer risk, the specific issue Plaintiffs allege Defendants should have warned of or otherwise referenced in their product labeling. This is clearly distinguishable from the facts presented and found insufficient for preemption in *Levine* and *Gaeta*. In *Levine*, the FDA lacked a meaningful review of the risk implicated by the plaintiff's claims, and in *Gaeta*, although the FDA had considered the general safety of ibuprofen, it had not considered the specific risk challenged by the plaintiffs. Though Plaintiffs argue the FDA's conclusion in the Assessment did not consider the totality of available scientific data, the Assessment

refutes this argument in light of the FDA's "comprehensive review" of "multiple streams of data" related to pancreatic safety. (Doc. No. 1163-3 at 4.)

In addition to considering the specific issue raised by Plaintiffs, the FDA has also consistently concluded that a causal association between the drugs and pancreatic cancer is indeterminate. This falls below the science-based regulatory standards that govern what must be included in product labeling. *See* 21 C.F.R. § 201.57(c)(6) (requiring reasonable evidence of a causal association); *id.* § 201.57(c)(7) (requiring some basis to believe there is a causal association). The FDA acknowledged as much in the Assessment by stating that product labeling was adequate, particularly as none of the drugs referenced pancreatic cancer. (*See* Doc. No. 1163-3 at 76–77.)

The FDA's subsequent inaction regarding drug labeling supports the conclusion that the FDA does not consider available scientific evidence of a causal association sufficient to warrant inclusion in the labeling. For example, the FDA has not communicated further regarding pancreatic cancer risk, or taken any actions inconsistent with its prior conclusion that the labeling is adequate. The FDA has also not required any of the Defendants to add a pancreatic cancer warning, or required the inclusion of a warning in newly approved incretin-based therapies. While FDA inaction is insufficient on its own to establish preemption, it is highly persuasive given the FDA's comprehensive review of pancreatic safety and ability to mandate a labeling change if it concluded the regulatory standards were satisfied.[15] *Cf. Gaeta*, 603 F. 3d at 1237 (noting

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[15] Defendants argue the 2007 amendment to the FDCA that gave the FDA explicit power to mandate a change in product labeling "changes the 'clear evidence' analysis." (Doc. No. 1289 at 4–5.) Plaintiffs take issue with this characterization and emphasize the difference between the FDA mandating a label change and the FDA permitting a label change submitted by a manufacturer. (*See* Doc. No. 1445 at 48:3–6.) While the Court does not find the 2007 amendment authorizing the FDA to mandate a label change alters the clear evidence analysis as set forth in *Levine*, the Court does find the FDA's failure to mandate a labeling change after reviewing data related to pancreatic cancer persuasive in reaching its conclusion that clear evidence exists.

Perrigo did not suggest it supplied the FDA with an evaluation of the specific issue raised by the plaintiffs' claims and that the FDA refused to act). That is not to say the Court's finding of clear evidence is solely based on the FDA's inaction. It is the FDA's failure to act coupled with its substantial review of the issue posed by Plaintiffs' claims that the Court finds persuasive.[16] When considered in its entirety, and in connection with federal regulatory standards governing product labeling, the record establishes the FDA would have rejected a pancreatic cancer label change, having found on more than one occasion that scientific evidence did not support such a reference.

In reaching its conclusion that clear evidence exists, the Court rejects Plaintiffs' position that Defendants cannot establish preemption absent express rejection of a proposed labeling change. Plaintiffs overstate the burden imposed by *Levine*, arguing Defendants can establish preemption only by proving: "*if* they had conferred with the FDA, and *if* they had provided an accurate analysis of the specific evidence concerning pancreatic cancer, and *if* they had submitted a properly-supported CBE, then the FDA would be so strongly opposed to the warning that it would reject the proposed warning and bring an unprecedented enforcement action against the Defendants." (Doc. No. 1165-1 at 13) (emphases in original). Though a CBE or PAS submission and rejection would readily meet the clear evidence standard, it is not the only means by which a manufacturer can establish conflict preemption. *See Reckis*, 471 Mass. at 290 n.29. ("The court in *Wyeth* specifically suggested that 'clear evidence' could be established by the FDA's rejection of a drug maker's attempt to give the warning underlying a claim of failure to warn. That is not to say that the *Wyeth* standard of clear evidence can be

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[16] Also notable is the timing of the FDA's reviews of pancreatic safety, which spanned from as early as 2009 through the end of 2014, encompassing the times when Plaintiffs in this multidistrict litigation were prescribed and consumed the drugs. This is different from cases such as *Mason* and *Koho* which recognized significant gaps in time between the FDA's review of a safety issue and the plaintiffs' failure to warn claims as precluding a finding the plaintiffs' claims were preempted.

satisfied only by the FDA's rejection of a manufacturer's request for an additional warning.").[17]

The language in *Levine* supports this conclusion. The Supreme Court stated a manufacturer must demonstrate by clear evidence the FDA *would* have rejected a label change, not whether the FDA *did* reject the labeling change sought by a plaintiff. Moreover, although *Levine* emphasized the importance of the CBE provision as related to a manufacturer's responsibility to maintain adequate labeling, Defendants do not argue the CBE provision is unavailable to them. Instead, and contrary to Wyeth's position in *Levine*, Defendants argue CBE submission is unnecessary as opposed to unavailable.

The authority Plaintiffs cite as support for this argument are unpersuasive as those cases do not present facts as compelling as the instant matter, and do not singularly analyze whether the manufacturer submitted a proposed warning that the FDA rejected. For example, in *Dobbs*, the court found submission of a pediatric suicidality warning and the FDA's rejection of that warning highly persuasive in finding the plaintiff's claims preempted. 797 F. Supp. 2d at 1277. However, the CBE submission was not specific to the plaintiff's claim, which focused on warning of an increased risk of suicide in adults. *Id.* In addition to the rejection of a pediatric suicide warning, the court also cited the FDA's consistent opinion that scientific evidence did not support a warning for adult patients in concluding the plaintiff's claims were preempted. *See id.* at 1276 ("More important in the context of this case, however, is the FDA's repeated refusal to extend suicidality warnings to adult patients over the age of 25."). Thus, while *Dobbs* found the FDA's rejection of a pediatric warning highly persuasive, it does not support the

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[17] Plaintiffs' bright line rule for conflict preemption requiring submission of a proposed label change is also contrary to the wealth of case law acknowledging the clear evidence standard remains undefined and requires a fact-intensive analysis. *See, e.g.*, *Gaeta*, 630 F.3d at 1235 ("The Court, however, did not clarify what would amount to 'clear evidence.' Rather, the only guidance this court has is that the evidence presented in *Levine* was insufficient to meet the clear evidence standard.").

conclusion that *Levine* requires a manufacturer to submit a label change to establish a plaintiff's claims are conflict preempted. *See also In re Fosamax (Alendronate Sodium) Products Liab. Litig.*, 951 F. Supp. 2d at 703 (finding preemption based on PAS submission, but recognizing the clear evidence standard is undefined); *In re Actos (Pioglitazone) Products Liab. Litig.*, No. 6:11MD2299, 2014 WL 4364832, at *20 (W.D. La. Sept. 2, 2014) (rejecting manufacturer's preemption defense in light of substantial evidence that the manufacturer rejected the FDA's efforts to require a stronger warning).

Moreover, although Plaintiffs argue a defendant must submit a CBE or PAS to warrant preemption, Plaintiffs do not establish the FDA's substantial review of pancreatic safety was different from what the FDA would have done in response to a CBE.[18] (*See, e.g.*, Doc. Nos. 1166-8 at 8; 1166-24 at 8) (explaining how the FDA evaluates new safety information and drug safety information). In fact, the record suggests the FDA's review of pancreatic safety was more thorough than a review of relevant data offered in connection with a CBE or PAS. Instead of reviewing data submitted by an individual manufacturer, the FDA considered a variety of data sources related to the entire class of incretin mimetics. It also conducted its own studies and reevaluated data submitted by manufacturers in reaching its conclusions. If Defendants *had* submitted a CBE or PAS, which the FDA subsequently rejected, clear evidence would exist and Plaintiffs' claims would be conflict preempted. The facts of this matter are different in form only. Although there was no CBE or PAS submission, the FDA conducted an independent review of pancreatic safety and concluded scientific evidence did not support any changes to the

[18] Plaintiffs do argue that the FDA affords deference to the views of a manufacturer, and that a "properly supported" CBE would establish either reasonable evidence of a causal association or some basis to believe there is a causal association. This deference, however, does not change the regulatory standard the FDA would apply in analyzing a manufacturer's CBE supplement. Regardless of what prompts the FDA's review of an issue, whether as part of initial drug approval, a CBE submission, or the FDA's own review of a safety signal, the same regulatory standard applies. (*See* Doc. Nos. 1163-3 at 82–83; 1164-4 at 123.)

product labeling. This is precisely what the FDA would have done upon receipt of a proposed warning by Defendants. In relying on the Assessment and the FDA's rejection of the Victoza citizen petition, Defendants offer more than a hypothetical assumption about what the FDA would have done in response to a pancreatic cancer label submission. *Cf. Dorsett*, 699 F. Supp. 2d at 1159 (finding the plaintiff's claims not preempted and noting "[d]efendants offer nothing but theoretical assumptions of what the FDA would have done, and that is not enough to warrant a finding of preemption"). The FDA's conclusions should not be subject to reevaluation simply because they were not articulated in connection with a CBE or PAS rejection.

For these reasons, the Court finds Defendants have established by clear evidence that the FDA would reject a pancreatic cancer labeling change, and that *Levine* does not require CBE submission and rejection. *See Robinson*, 615 F.3d at 873 ("The FDA decided not to require such a warning . . . and a court cannot order a drug company to place on a label a warning if there is 'clear evidence' that the FDA would not approve it.").

D. The FDA has expressed its official position regarding pancreatic safety

Plaintiffs assert the Assessment, citizen petition response, and Saxenda briefing document do not represent the FDA's official position regarding the pancreatic safety of incretin mimetics. Plaintiffs cite to a recent Ninth Circuit case, *Reid v Johnson & Johnson*, 780 F.3d 952, 955 (9th Cir. 2015), in arguing statements by FDA staff members and the FDA itself are not entitled to preemptive effect if those statements lack the force and effect of law.

In *Reid*, the Ninth Circuit considered whether a plaintiff's claims were conflict preempted under the Federal Food, Drug, and Cosmetics Act as related to nutritional labeling on food products. The court in *Reid* reiterated that a "federal agency acting within the scope of its congressionally delegated authority may . . . render unenforceable state or local law." The Ninth Circuit then went on to analyze whether an FDA letter was entitled to preemptive effect, and in doing so, analyzed when agency action is entitled to

controlling weight. *See id.* at 964 (citing to *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843–44 (1984) and *United States v. Mead Corp.*, 533 U.S. 218, 234 (2001)). The preemption analysis set forth in *Reid* is inapplicable in this matter, and the Court does not view the parties as arguing *Reid* provides a relevant conflict preemption standard. *Reid* is relevant, however, with respect to whether the FDA was acting in the course of its congressionally delegated authority in reviewing and commenting on the pancreatic safety of incretin mimetics. If answered affirmatively, the FDA action in this case would be entitled to preemptive effect. Thus, the appropriate question is whether the FDA was acting within the scope of its regulatory authority in reviewing pancreatic safety and commenting on the labeling of incretin mimetics.

The FDA's review of pancreatic safety data of the drugs at issue falls squarely within the FDA's congressionally delegated authority to regulate the safety of prescription drugs. The Assessment exemplifies the FDA's approach in discharging its regulatory duties. Four FDA officials authored the Assessment, and the Assessment is identified as coming from the FDA's Office of New Drugs, Center for Drug Evaluation and Research. Additionally, the Assessment is written from the FDA's perspective and lacks the disclaimer required when publications of FDA employees do not necessarily reflect the opinions of the agency. (*See* Doc. No. 1163-4 at 98) (noting all non-assigned FDA-related articles or speeches must include a disclaimer stating the article "reflects the views of the author and should not be construed to represent FDA's views or policies"). Plaintiffs' regulatory expert acknowledges the Assessment represents the FDA's official position regarding pancreatic safety. (Doc. No. 1163-3 at 85:1–16.) Similarly, responding to citizen petitions is within the FDA's regulatory authority. The Victoza citizen petition rejection was written by the Director of the FDA's Center for Drug Evaluation and Research, and constitutes the FDA's official response to the request to withdraw Victoza from the market. Other courts to address conflict preemption have considered citizen petition responses as indicative of whether the FDA would reject a proposed labeling

change. *See, e.g.*, *Mason*, 596 F.3d at 395 (considering citizen petitions in clear evidence analysis); *Koho*, 17 F. Supp. 3d at 1117 (same); *Dorsett*, 699 F. Supp. 2d at 1157 (same).

With respect to the Saxenda briefing document, Plaintiffs note the prominent disclaimer that the information contained within the document may not represent the FDA's official position. (*See* Doc. No. 1219-2 at 4) (stating the conclusions and recommendations in the document "do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office" of the FDA). However, the document contains the same conclusion regarding a causal relationship as that expressed in the Assessment and the citizen petition response, namely that a causal association between the drugs and pancreatic cancer had yet to be established. Thus, even if the FDA did not intend the Saxenda briefing document to be an official representation of the FDA's opinion, it is relevant to the clear evidence analysis to the extent it confirms the FDA's previously expressed conclusions.

As such, the Court finds the Assessment and citizen petition response constitute the FDA's official position regarding pancreatic safety, as both fall within the FDA's congressionally delegated regulatory authority. The Court therefore properly considers the FDA's conclusions regarding a causal association between incretin mimetics and pancreatic cancer, and its statements specific to the adequacy of product labeling, as the basis of Defendants' preemption defense.

E. The FDA's ongoing review of pancreatic safety and the existence of a pancreatic cancer safety signal do not preclude preemption

Plaintiffs also argue the FDA has not reached a final conclusion about the pancreatic safety of incretin mimetics, and that the FDA's pancreatic cancer safety signal remains open. According to Plaintiffs, the open safety signal indicates there is some basis to believe there is a causal association, and thus Defendants should have included pancreatic cancer as an adverse reaction in product labeling.

Although Plaintiffs place significant weight on these facts, the existence of an open safety signal and the FDA's ongoing review of pancreatic safety do not undermine the FDA's previously articulated conclusions. The existence of a safety signal is not, without more, indicative of a causal association. FDA Guidance for Industry recognizes that "signal generation is [] only the first step in pharmacovigilance and indicates the need for further investigation *before any conclusions are drawn*." (Doc. No. 1163-4 at 128) (emphasis added). Defendants' expert similarly acknowledged, "a safety signal generated through adverse event data mining is simply an indication that a drug might be associated with a particular risk and that further study is warranted," and that "[i]n general, a safety signal is not itself evidence of a causal association between a drug and an adverse event." (Doc. No. 1163-4 at 128; *see also* Doc. No. 1215 at 15 n.41) ("[Safety] [s]ignals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.").

To warrant inclusion in product labeling the FDA must conclude, at a minimum, that there is some basis to believe there is a causal relationship between the drug and the adverse reaction. The existence of a hypothetical causal association is insufficient to satisfy this standard. *See Robinson*, 615 F.3d at 869 (noting a label describing every serious disease that might or even arguably be caused by a drug would result in "information overload" making "label warnings worthless to consumers"); *Mason*, 596 F.3d at 392 ("While it is important for a manufacturer to warn of potential side effects, it is equally important that it not overwarn because overwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted and can dilute the effectiveness of valid warnings.").[19]

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[19] Plaintiffs also reference examples in the record where either the FDA or Defendants have expressed concern about pancreatic cancer risk. (*See, e.g.*, Doc. Nos. 1165-16 at 5;

Additionally, the Court finds the FDA's ongoing review of pancreatic safety more indicative of the evolving nature of drug surveillance, than of the existence of a causal association. Defendants' expert stated, "as a matter of routine practice, FDA continuously monitors every medication for new or evolving information as long as a drug is on the market." (Doc. No. 1163-4 at 115).[20] In *Levine*, the Supreme Court acknowledged the same in noting that the CBE regulation "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Levine*, 555 U.S. at 569. The potential for the FDA to reach a different conclusion in the future in light of new scientific evidence or developments does not preclude a finding of preemption now. Although the Assessment concluded the FDA had not reached a final conclusion regarding pancreatic safety, whether the FDA will definitively conclude the drugs do or do not cause or create an increased risk of pancreatic cancer is unknown. Because the Court is required to analyze conflict preemption in the context of the current record, the FDA's ongoing review does not undermine the FDA's current conclusions.

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1219-5 at 9.) The Court finds these examples reinforce that both the FDA and Defendants have been aware of and considered pancreatic cancer risk, and the Court does not assign the same negative connotation to that acknowledgement as Plaintiffs.

[20] Plaintiffs challenge the expert opinion offered by Dr. Lawrence Goldkind in support of Defendants' motion for summary judgment because his opinion is contrary to *Levine*. (Doc. No. 1285 at 7) (citing *In re Trasylol Products Liab. Litig.*, No. 08MD01928, 2010 WL 4259332, at *1 (S.D. Fla. Oct. 21, 2010)). Although a party may challenge the expert testimony offered in connection with a motion for summary judgment, Plaintiffs' challenge is limited to Dr. Goldkind's description of FDA labeling that is contrary to *Levine*, and his opinion about the possibility that the FDA would reject a CBE. (Doc. No. 1285 at 7.) Because of the FDA's extensive action specific to Plaintiffs' claims, the Court does not rely on Dr. Goldkind's opinion regarding whether the FDA would reject a CBE, and otherwise does not find his opinion is contrary to *Levine*.

F. New safety information and the relevance of Buckman v. Plaintiffs' Legal Committee

A central theory in Plaintiffs' opposition to preemption is that new safety information exists that could support a labeling change. Plaintiffs first raised this argument in the context of preemption discovery through allegations that Defendants withheld, misrepresented, or underrepresented data related to pancreatic cancer risk from the FDA. Plaintiffs raise the same argument in the instant motions, asserting Defendants failed to provide the FDA with data supportive of a causal connection between the drugs and pancreatic cancer. According to Plaintiffs, because the FDA has not considered this information, Defendants cannot establish conflict preemption.

With respect to Merck, Plaintiffs contend the FDA did not receive or consider a ninety-eight page signal assessment completed by Health Canada regarding the pancreatic safety of incretin mimetics. The signal assessment found the "use of Januvia may be associated with an increased risk of cancer of the pancreas." (Doc. No. 1164-3.)

Plaintiffs also contend Merck and Novo did not provide the FDA with evidence of a pancreatic cancer imbalance in clinical trials. Plaintiffs cite to the FDA's reliance on a published study by a Merck employee, the results of which excluded three known cases of pancreatic cancer in patients that had taken Januvia. (Doc. No. 1165-6.) Similarly, Plaintiffs argue the annual review submitted to the FDA by Novo in August 2013 underrepresented clinical trial imbalances. (Doc. Nos. 1165-8; 1165-9.) Lastly, with respect to Novo, Plaintiffs argue Novo did not provide the FDA with its secondary internal analysis conducted on results from a 13-week study of ZDF rats. In the results submitted to the FDA, Novo represented there were "no effects of liraglutide or exenatide on overall pancreas weight or exocrine and duct cell mass proliferation," and that "no effect on the exocrine pancreas" was detected. (Doc. No. 1166-21.) A secondary analysis of the data, however, suggested liraglutide "has some effect on [pancreatic ductal gland] mass proliferation." (Doc. Nos. 1165-1 at 23; 1165-13.)

Finally, Plaintiffs contend Amylin and Lilly did not provide the FDA with evidence of precancerous lesions observed in primate studies. Based on the blinded analysis conducted by one of Plaintiffs' experts, Plaintiffs contend that information published and presented to the FDA omitted data demonstrating "overt pancreatic toxic effects" including an increased occurrence of PanIN lesions. (Doc. No. 1165-11.)

Plaintiffs argue the above data constitutes new safety information within the meaning of federal labeling regulations, thereby triggering Defendants obligation to provide that information to the FDA. In response, Defendants argue there is no evidence the data would be material to the FDA's conclusion regarding pancreatic safety, or that the data would alter the FDA's position regarding the adequacy of product labeling. After thorough consideration of Plaintiffs' arguments in the context of FDA regulations, and the information at issue, the Court maintains its position as set forth in previous orders regarding the relevance of this data to the Court's conflict preemption analysis.

In the context of preemption discovery, the Court ruled it could not entertain allegations that Defendants misreported or underreported information to the FDA regarding pancreatic cancer risk. (*See* Doc. No. 705.) Relying on the policy underlying the Supreme Court decision of *Buckman v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), the Court declined to compel discovery and concluded that Plaintiffs' misreporting and underreporting arguments were preempted. Plaintiffs contended then and in the context of the current motions that *Buckman* is not applicable. Though *Buckman* does not govern whether Plaintiffs' failure-to-warn claims are conflict preempted, the Court finds *Buckman* implicated by Plaintiffs' defense to the clear evidence standard.

In *Buckman*, the Supreme Court concluded that fraud-on-the-FDA claims were preempted because they "inevitably conflict with the FDA's responsibility to police fraud." *Id.* at 350. The Supreme Court therefore held that a plaintiff's state law claim premised solely on allegations of misreporting or underreporting information to the FDA is preempted. As support for its conclusion, *Buckman* noted such claims conflict with the

federal statutory scheme that empowers the FDA to deter fraud, and the increased and inconsistent burdens such claims would assert on drug manufacturers. *Id.* (noting such claims would "dramatically increase the burdens facing potential applicants—burdens not contemplated by Congress" and "cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court").

Plaintiffs cite two cases in support of the argument that claims a defendant withheld information from the FDA are not preempted under *Buckman* and operate to bar a finding of conflict preemption. The cases, however, are readily distinguishable. The first case, *In re Actos Products Liability Litigation*, presents far more egregious facts than those implied by Plaintiffs in this matter. *Actos* involved the defendants' ongoing attempts to preclude the FDA from including a bladder cancer warning in product labeling. *See* 2014 WL 4364832, at *20 (noting the defendants actively attempted "***to prevent*** *the FDA from including any warning* about bladder cancer on the Actos label" and "*engaged in substantial negotiations with the FDA* ***to prevent the inclusion*** *on the label of any warning about bladder cancer*") (emphases in original). Plaintiffs in this matter do not allege Defendants actively engaged in a campaign to deceive or mislead the FDA, or to prevent the inclusion of a pancreatic cancer reference in product labeling. Additionally, in *Actos*, the facts suggested the FDA concluded the labeling was inadequate and sought the manufacturers help in creating an appropriate label. *Id.* The FDA has made no such overtures in this case, instead concluding multiple times that current product labeling adequately reflects scientific data.

Similarly, the court in *In re Fosamax Products Liability Litigation* did note in finding preemption that the plaintiff did not argue the defendants had failed to provide all of the information it had about the relevant injury to the FDA. 951 F. Supp. 2d at 705. Such an assertion in this case, however, does not automatically preclude preemption. The Court maintains its earlier position that such arguments are preempted to the extent they are based on Defendants failure to comply with FDA reporting requirements. *See*

Rheinfrank, 2015 WL 4743056, at *11–12 ("Plaintiffs' argument that Abbott withheld certain information or misrepresented the results of studies in its 2005 and 2007 submissions to the FDA appears to be a fraud-on-the-FDA theory, which is preempted."). *Fosamax* does not convince the Court that such claims are properly considered in light of *Buckman*, or that asserting Defendants misreported or underreported information to the FDA militates against a finding of clear evidence. Thus, although Plaintiffs reframe this data as new safety information, the Court declines to consider it as undermining the FDA's conclusion in the Assessment and citizen petition response.

As additional support for this conclusion, the Court notes that it remains unclear whether the FDA considered this information, and if it did not, whether this data would have altered the FDA's conclusion. The parties' experts dispute whether the information was material to the FDA's analysis and offer little clarity on this point. However, as noted at the hearing on these motions, it is unlikely that a conflict preemption proponent, or a plaintiff opposing the defense, would ever know the full extent of what the FDA reviewed in evaluating a safety signal. Under Plaintiffs' reasoning, a plaintiff could always cite to a particular piece of data, presumably unconsidered by the FDA, and overcome conflict preemption. A reevaluation of scientific data or a judicial challenge to the accuracy of the FDA's conclusions would disrupt the "delicate balance of statutory objectives" the *Buckman* Court sought to preserve. *Buckman Co.*, 531 U.S. at 351 (noting fraud-on-the-FDA claims "would exert an extraneous pull on the scheme established by Congress, and it is therefore pre-empted by that scheme").

Lastly, Plaintiffs cite to *Levine* and *Gaeta* and argue throughout their briefing that there is no evidence the FDA considered this allegedly withheld or misrepresented data. *Levine*, however, does not mandate which data the FDA must consider in evaluating a safety signal or labeling change. The relevant consideration is whether the FDA considered the *safety concern* challenged by a plaintiff—IV push versus IV drip administration of Phenergan in *Levine*, and concomitant use of ibuprofen and other drugs known to cause liver toxicity in *Gaeta*. Courts have not addressed the specific data relied

on by the FDA in reaching its conclusion. What the FDA considers in evaluating a safety signal is best left to the discretion of the FDA and not subject to challenge as part of a preemption analysis. Thus, Plaintiffs' challenges to the completeness of the FDA's conclusions, the data it considered, and the weight it afforded such data are not persuasive or appropriate considerations in analyzing the clear evidence standard.

In this respect, the Court must also afford deference to the FDA's repeated conclusion that analyses of adverse event data and spontaneous reporting is not illustrative of a causal relationship. Throughout its review of pancreatic cancer risk, the FDA has consistently rejected adverse event data as illustrative of a causal association. (*See, e.g.*, Doc. Nos. 1163-4 at 79, 90; 1163-3 at 3); *see also Dobbs*, 797 F. Supp. 2d at 1273 (noting in its preemption analysis that the FDA did not consider individual manufacturer's reports of adverse events sufficiently persuasive to provide "reasonable evidence of an association" between the drug and the reported adverse consequence). At oral argument, Plaintiffs challenged this conclusion as well, by citing to studies indicating a greater significance of adverse event data in connection with a proliferation theory of pancreatic cancer risk. (Doc. No. 1445 at 113–114, 118, 122–123.)[21] This argument is unpersuasive for the same reason noted above. Although Plaintiffs indicated such a

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[21] The cell proliferation theory is Plaintiffs' dominant theme. Indeed, this theory was specifically considered by the FDA in Assessment. (*See* Doc. No. 1163-3 at 3 ("These studies included extensive histopathological evaluation of the endocrine and exocrine pancreas, including analysis of ductal morphology and histochemical staining capable of disclosing pathological proliferation and apoptosis."); *see also* Doc. No. 1163-4 at 89 (noting no adverse effect on exocrine histology or proliferation).) A secondary theme of Plaintiffs is the lack of tests before the FDA on animal specimens more typical of diabetic patients, *e.g.*, overweight or obese specimens. Again, the Assessment belies this assertion by specifically commenting on FDA-mandated pancreatic toxicity studies performed in a rodent model of diabetes. (*See* Doc. No. 1163-3 at 3.) Finally, Plaintiffs argue the inclusion of pancreatitis in product labeling is evidence the FDA would permit Defendants to reference pancreatic cancer. It does not follow, however, that a reference to pancreatitis supports reference to a pancreatic cancer, particularly in light of the FDA's repeated conclusions to the contrary.

theory suggested stronger evidence of a causal association, they also admitted that the FDA considered that theory, but gave it "no weight" in their overall analysis. (Doc. No. 1445 at 124:24–25.) Plaintiffs in essence request the Court to substitute Plaintiffs' evaluation of scientific data for that of the FDA's. If the FDA was not as active in investigating pancreatic cancer risk, and as consistent in its conclusion that a causal association is indeterminate, the Court could find Plaintiffs' arguments weighed against preemption. However, the FDA's extensive evaluation of pancreatic cancer risk forecloses such consideration or reevaluation of what the FDA considered or how it reached its conclusions.

In light of the foregoing, the existence of new safety information does not alter the Court's conclusion that clear evidence exists that the FDA would have rejected a pancreatic cancer label change at the time Plaintiffs' claims accrued.

V. CONCLUSION

As set forth above, Defendants have demonstrated by clear evidence that the FDA would have rejected a reference to pancreatic cancer in the product labeling during the time in which Plaintiffs' claims accrued. Plaintiffs' challenges to the FDA's conclusions regarding pancreatic cancer risk are insufficient to overcome preemption in light of the extensive regulatory history of the drugs at issue. The evidence establishes the FDA has reviewed the risk specific to Plaintiffs' claims and, after considering the totality of available scientific data, concluded a warning or other reference to that risk is unsubstantiated. Accordingly, the Court **GRANTS** Defendants' motion for summary judgment and **DENIES** Plaintiffs' cross-motion for summary judgment.

The scope of the Court's order on preemption applies to Plaintiffs' claims that accrued any time before the date the record closed on the instant motions for summary judgment.[22] Other courts to address conflict preemption in the pharmaceutical drug

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[22] Although the Court heard oral argument on September 11, 2015, the Court permitted the filing of additional briefing from the state court proceedings, which the parties filed in

context have found FDA action immediately before, during, and after the time a plaintiff's claim accrued relevant to a preemption analysis.[23] Finding no significant temporal gaps between the FDA's conclusions regarding pancreatic cancer risk and the dates Plaintiffs' claims accrued, the Court finds such claims preempted. Though the most compelling example of clear evidence the FDA would have rejected a pancreatic cancer label change occurred in 2014, the record supports the conclusion that a label change would have been rejected at any earlier date, when presumably less scientific data existed, and less extensive research by the FDA had been conducted. This is particularly true as the FDA's earliest conclusions regarding pancreatic cancer risk as presented in the record occurred in 2009. Thus, the affirmative defense of preemption operates to bar Plaintiffs' claims which accrued prior to the close of the record.

IT IS SO ORDERED.

Dated: November 9, 2015

Hon. Anthony J. Battaglia
United States District Judge

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this matter on October 15, 2015. Thus, the Court considers October 15, 2015, the date the record closed for the purposes of its preemption finding.

[23] *See Rheinfrank*, WL 4743056, at *10 ("The Court finds the FDA's February 2006 decision that developmental delay warnings 'should not be incorporated into [Depakote] labeling' and the FDA's 2008 belief that 'the data do not provide sufficient evidence to support [Depakote] labeling changes at this time' constitute 'clear evidence' that when confronted by the issue in 2003, the FDA would have rejected an attempt to add a developmental delay warning."); *Dobbs*, 797 F. Supp. 2d at 1275 (considering the FDA's actions from 1993 through 2007 in evaluating whether a warning would have been approved in 2002).