**WILLIAMS & CONNOLLY LLP**
Douglas R. Marvin (SBN 933671)
F. Lane Heard, III (SBN 291724)
Ana C. Reyes (SBN 477354)
Paul E. Boehm (SBN 493245)
725 Twelfth Street, N.W.
Washington, DC 20005
Telephone: (202) 434-5000

*Attorneys for Merck Sharp & Dohme Corp.*

**PEPPER HAMILTON LLP**
Nina M. Gussack (SBN 31054)
Aline Fairweather (SBN 79744)
Kenneth J. King (SBN 1885961)
3000 Two Logan Square
Eighteenth and Arch Streets
Philadelphia, PA 19103
Telephone: (215) 981-4000

*Attorneys for Eli Lilly and Company*

**WILSON TURNER KOSMO LLP**
Vickie E. Turner (SBN 106431)
550 West C Street, Suite 1050
San Diego, California 92101
Telephone: (619) 236-9600

*Attorneys for Merck Sharp & Dohme Corp.*

**DLA PIPER LLP (US)**
Loren H. Brown (SBN 2533529)
Heidi Levine (SBN 2822740)
Raymond M. Williams (SBN 164068)
1251 Avenue of the Americas
27th Floor
New York, NY 10020
Telephone: (212) 335-4500

*Attorneys for Novo Nordisk Inc.*

**O'MELVENY & MYERS LLP**
Richard B. Goetz (SBN 115666)
Amy J. Laurendeau (SBN 198321)
400 South Hope Street
Los Angeles, CA 90071
Telephone: (213) 430-6000

*Attorneys for Amylin Pharmaceuticals, LLC*

**UNITED STATES DISTRICT COURT**

**FOR THE SOUTHERN DISTRICT OF CALIFORNIA**

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

**MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION**

Date: September 11, 2015
Time: 9:00 am
Courtroom: 3B
Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

# TABLE OF CONTENTS

# TABLE OF AUTHORITIES

## FEDERAL CASES



## OTHER AUTHORITIES

## INTRODUCTION

Defendants move for summary judgment on the grounds that federal law preempts Plaintiffs' state law failure-to-warn claims. Plaintiffs claim that Defendants failed to warn about the (supposed) risk of pancreatic cancer for each of the medications—Byetta, Januvia, Janumet, and Victoza—Plaintiffs were prescribed for the treatment of diabetes. The question raised by this motion is whether there is clear evidence that the Food and Drug Administration (FDA) would have refused to approve Plaintiffs' proposed labeling change.

There is such clear evidence, for FDA has taken a series of deliberate actions to acknowledge published concerns about a possible risk, to carry out a thorough study of the issue, and then to make a very public declaration of its findings and conclusion that the current labeling is adequate. FDA has considered the very claim asserted by Plaintiffs in this litigation—namely, that the labeling for Byetta, Januvia, Janumet, and Victoza should warn about a risk of pancreatic cancer. It has conducted its own comprehensive evaluation of the scientific evidence concerning pancreatic cancer. And, in what Plaintiffs' own expert Dr. Alexander Fleming calls an "unprecedented" publication, FDA has explicitly rejected Plaintiffs' scientific claim in an official statement, published in the February 2014 issue of *The New England Journal of Medicine* (NEJM).[1]

FDA said clearly in NEJM that (i) the scientific data do not support a causal association between the medications and pancreatic cancer, (ii) there is no evidence that would support a change to the existing labels, and (iii) the current warnings are adequate:

> [A]ssertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer, as recently

[1] Amy G. Egan et al., *Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment*, N. Engl. J. Med. 370:9 (Feb. 27, 2014) ("FDA/EMA Assessment") (attached as Ex. A to the Declaration of Amy J. Laurendeau ("Laurendeau Decl.")).

> expressed in the scientific literature and in the media, are *inconsistent* with the current data. . . . . *[T]he current knowledge [regarding safety risks] is adequately reflected in the product information or labeling.*[2]

Subsequent developments confirm FDA's clear position. In March 2014, FDA rejected a Public Citizen petition regarding Victoza.[3] The Petition had asked FDA to withdraw Victoza from the market, based in part on a claim that patients being treated with the medication faced an increased risk of pancreatic cancer.[4] Noting that it had "carefully considered the information submitted in the Petition, the comments submitted to the docket, and other data identified by the Agency,"[5] FDA denied the Petition because the data offered "no new evidence regarding the risk of pancreatic carcinoma that would support *any changes to the current approved labeling*."[6]

Then, in September 2014, in a Briefing Book prepared for the Advisory Committee assessing the safety and efficacy of Saxenda (a higher dose of liraglutide (Victoza) for use in weight management), FDA said: (1) "Risk for pancreatic cancer has more recently emerged as a concern with GLP-1-based therapies, including liraglutide. … However, *animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association*";[7] and (2) "Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, *do not support*

---

[2] *Id.* at 795–96 (emphasis added). The FDA/EMA Assessment refers to the medications in this litigation by their active ingredients: exenatide (Byetta), sitagliptin (Januvia and Janumet), and liraglutide (Victoza).

[3] Letter from Janet Woodcock, Dir., FDA Ctr. for Drug Evaluation & Research, to Elizabeth Barbehenn & Sidney M. Wolfe, Public Citizen's Health Research Grp. (Mar. 25, 2014) ("Public Citizen Letter") (attached as Ex. B to Laurendeau Decl.).

[4] Public Citizen Letter (Ex. B) at 26.

[5] *Id.* at 1.

[6] *Id.* at 26 (emphasis added).

[7] FDA Briefing Document, NDA 206321 (Sept. 11, 2014) at 117 ("Saxenda Briefing Book") (emphasis added) (relevant portions attached as Ex. C to Laurendeau Decl.). The Briefing Book represents FDA's analysis of the drug's safety and efficacy in advance of the Advisory Committee meeting.

*pancreatic cancer as an incretin mimetic-mediated event*."[8] In December 2014, FDA approved the label for Saxenda without any reference to pancreatic cancer. In fact, between February and December 2014, FDA approved labels without information about pancreatic cancer for four new incretin-based therapies.[9]

This sequence of events constitutes clear evidence that FDA (i) focused its attention on the very issue raised by Plaintiffs, (ii) carried out an extensive review and analysis of the scientific evidence, (iii) drew the conclusion that the scientific evidence did not warrant any change in the labeling (specifically, not the addition of safety information about pancreatic cancer), (iv) in early 2014, published that conclusion as the Agency's official position, and (v) reiterated that conclusion in later, related regulatory actions. The facts here, in other words, are the very facts that the Supreme Court found missing in the *Wyeth v. Levine* record and that the Ninth Circuit found missing in the record in *Gaeta v. Perrigo Pharmaceuticals Co.*, 630 F.3d 1225 (9th Cir. 2011). Plaintiffs have argued that preemption arises only when a manufacturer proposes a labeling change and FDA rejects it. But this argument ignores the Supreme Court's recognition in *Wyeth* that federal law preempts state law when there is clear evidence showing that FDA *would have* rejected a labeling change, not that it *did* reject such a change.

The following material facts are undisputed: (1) FDA took note of, and considered, "assertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer, as recently expressed in the scientific literature and in the media"; (2) FDA conducted a years-long study of the scientific data concerning those assertions; (3) FDA published the findings and conclusions of its study in the NEJM; and (4) FDA said that "the current knowledge [regarding safety risks] is adequately reflected in the product information or labeling." Plaintiffs' expert Dr. Fleming does

---

[8] *Id*. at 313 (emphasis added).

[9] *See infra* p. 7 n.18.

not dispute these facts, nor does he dispute the ultimate conclusion about what FDA would do, given the undisputed facts. He disagrees with the scientific conclusions that FDA has made based on the data—a matter irrelevant to the Court's preemption inquiry—but he agrees that it would be "absurd" to conclude that FDA would say, "We've looked at all the data, we've done a comprehensive evaluation, we don't think there's any evidence of causal association, but go ahead and add a warning anyway."[10]

Whether these undisputed facts constitute clear evidence that FDA would have refused to approve a pancreatic-cancer warning is a question of law reserved to the Court. For the reasons given in the Argument section below, the Court should find that these facts, which reflect unprecedented action on the Agency's part to provide clarity for doctors and patients using incretin-based therapies, do constitute clear evidence that FDA would not have approved a labeling change regarding pancreatic cancer. Permitting Plaintiffs' state-law claims to proceed would revive the very confusion and uncertainty FDA has sought to eliminate. If ever there was clear evidence that FDA would have rejected a labeling change, it is this case.

## THE FACTS

In June of 2014, this Court denied Defendants' summary judgment motion, without prejudice, to permit Plaintiffs to pursue discovery related to preemption. (Doc. No. 472). Plaintiffs have now completed that discovery, which has not changed the material, undisputed facts. Those facts are as follows:

1. This MDL proceeding includes claims involving medications approved by FDA for the treatment of type-2 diabetes. The medications—Byetta, Januvia, Janumet, and Victoza—are broadly referred to as "incretin-based therapies" because they increase the levels of certain incretin hormones, which help lower blood sugar by stimulating production of insulin. More than 25 million people in the United States

[10] Fleming Tr. 201:21-202:1 (relevant portions attached as Ex. D to Laurendeau Decl.).

alone—or just under 1 in 10—suffer from type-2 diabetes.[11]

2. Incretin-based therapies are an approved treatment option for patients with type-2 diabetes. All leading medical organizations in the diabetes field recommend them.[12] It is important that different treatment options be available, because, given the chronic nature of the disease, persons suffering from type-2 diabetes often require different medications over time to control their blood sugar.

3. The medications at issue are, or at one time were, developed and/or distributed by Defendants Amylin Pharmaceuticals, LLC (Amylin), Eli Lilly and Company (Lilly), Merck Sharp & Dohme Corp. (Merck), and Novo Nordisk Inc. (Novo). Amylin manufactures Byetta, which was the first of these medications to obtain FDA approval (approved on April 28, 2005). Lilly previously collaborated with Amylin to promote this medication. Merck manufactures Januvia (approved on October 16, 2006) and Janumet (approved on March 30, 2007); and Novo manufactures Victoza (approved on January 25, 2010).[13]

4. Under the Federal Food, Drug, and Cosmetic Act, Congress has committed regulatory authority over the approval and sale of prescription medications to FDA, including considerable authority over the content of prescription medication labeling. 21 U.S.C. § 355(d), (o); 21 C.F.R. pt. 201. Pharmaceutical manufacturers must submit proposed labeling to FDA as part of the new drug-approval process, and FDA must approve any labeling changes that become necessary in light of post-approval studies or experience. 21 C.F.R. § 314.70.

5. When FDA approved the incretin-based therapies as safe and effective,

---

[11] *See* FDA/EMA Assessment (Ex. A) at 794.

[12] *See generally* June 28, 2013 Statement of the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation ("ADA/EASD/IDF Statement") (attached to Laurendeau Decl. as Ex. E).

[13] *See* FDA Approval Letters for Byetta, Januvia, Janumet, and Victoza (attached to Laurendeau Decl. as Exs. F, G, H, and I, respectively).

the Agency necessarily also approved labeling, including warnings and adverse reactions, for the medications. Under federal law, a manufacturer cannot warn of suspected risks or identify adverse reactions that are not scientifically substantiated. FDA can only approve a warning as part of the labeling if there is "reasonable evidence" of a causal association between the medication and a particular risk. 21 C.F.R. § 201.57(c)(6). To include information about a risk in the "Adverse Reactions" section of the label, as opposed to a "Warning," there must be "some basis to believe there is a causal relationship" between a medication and a potential risk. 21 C.F.R. § 201.57(c)(7). These rules recognize that "[w]hile 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."[14]

6. In order to ensure that labeling promotes, rather than impedes, federal safety goals, FDA has imposed the following further limits on what may be included in labeling:

- "Labeling is not intended to be a dispositive treatise of all possible data and information about a drug."[15]
- Inclusion of "substantial differences of opinion among experts" or "other serious medical controversies" concerning labeling statements "would result in uncertainty and confusion, and, accordingly, decrease the usefulness of the warnings in protecting the public."[16]

---

[14] *Mason v. Smithkline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) (cited approvingly by *Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225, 1235 (9th Cir. 2011), *vacated on other grounds sub nom. L. Perrigo Co. v. Gaeta*, 132 S. Ct. 497 (2011)).

[15] Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,441 (June 26, 1979).

[16] *Id*. at 37,448.

- Inclusion in "drug labeling of medical or scientific controversy concerning labeling would be highly confusing, and thus misleading, in violation of section 502(a) of the act."[17]

7. When FDA approved Byetta, Januvia, Janumet, and Victoza as safe and effective, it did not require the labeling for those medications to warn about a pancreatic cancer risk. Nor did the Agency require a pancreatic cancer labeling change when it later approved each of eight other incretin-based therapies as safe and effective medications for the treatment of diabetes, including four approvals in 2014—a new extended release formulation of Bydureon (exenatide) on February 28, 2014, Tanzeum (albiglutide) on April 15, 2014, Trulicity (dulaglutide) on September 18, 2014, and Saxenda on December 24, 2014.[18] And since their initial approval, FDA has repeatedly approved labeling updates for Byetta, Victoza, and Januvia without requiring the manufacturers to provide pancreatic cancer warnings. These affirmative decisions to maintain the existing labels followed extensive analysis of whether these medications can cause pancreatic cancer—the specific issue in this litigation.

8. For many years, FDA has monitored the pancreatic safety of incretin-based therapies and evaluated whether there is a potential risk of pancreatic cancer. On September 17, 2009, the FDA Division of Metabolic and Endocrine Products asked the FDA Office of Surveillance and the Epidemiology Division of Pharmacovigilance to review its adverse event reporting database for cases of

---

[17] *Id*. at 37,455; *accord* Labeling: Failure To Reveal Material Facts, 39 Fed. Reg. 33,229, 33,231 (Sept. 16, 1974) ("Although [warnings] are often the subject of intense debate, [FDA] has never permitted drug labeling to reflect such debate."); *see id*. at 33,232.

[18] FDA approved Onglyza (saxagliptin) in 2009; Tradjenta (linagliptin) in 2011; Bydureon (extended release exenatide) in 2012; Nesina (alogliptin) in 2013. The FDA Approval Letters for Onglyza, Tradjenta, Bydureon, Nesina, Bydureon (extended release), Tanzeum, Trulicity, and Saxenda are attached as Exhibits J, K, L, M, N, O, P, and Q respectively, to the Laurendeau Declaration.

pancreatic cancer in Januvia and Byetta users.[19] In fulfilling this request, the Epidemiology Division searched the database and conducted a literature review using the National Health Institute database of publications.[20] FDA concluded that "little inference for risk [could be] appreciated from review of spontaneous reports of pancreatic cancer in adult recipients of anti-diabetics agents," because pancreatic cancer is "relatively common" in adults.[21]

9. On October 30, 2009, when FDA approved Byetta for use as monotherapy, FDA required Amylin to conduct pancreatic safety studies of Byetta, including epidemiologic queries to assess the relative risk of pancreatic cancer among patients using Byetta and patients using metformin or glyburide.[22]

10. Following assertions of pancreatic safety issues by a small group of academic researchers at UCLA, FDA announced, in March 2013, that it would conduct a comprehensive evaluation of these issues. FDA said that it would consider the totality of available scientific data, as well as the Agency's own "further investigat[ion] [into the] potential pancreatic toxicity associated with the incretin

---

[19] *See* Memorandum from John Bishai, Ph.D., Regulatory Project Manager, FDA, DMEP, to Millie Wright, FDA, Office of Safety and Epidemiology (Sept. 17, 2009) (attached as Ex. R to Laurendeau Decl.).

[20] *See* Memorandum from Allen Brinker, Team Leader, FDA Div. of Pharmacovigilance 1, to Mary Parks, Dir., FDA Div. of Metabolism & Endocrinology Prods., at 2 (Dec. 10, 2009) (attached as Ex. S to Laurendeau Decl.). Both this memorandum and the memorandum from Dr. Bishai were obtained in response to a Freedom of Information Act request made to FDA. They confirm that FDA paid more than "passing attention" to the question of pancreatic cancer, and has paid such attention for more than five years.

[21] *Id*. at 8.

[22] *See* Food and Drug Administration, *Byetta Safety Update for Healthcare Professionals* (Nov. 9, 2011), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190406.htm (last visited June 18, 2015).

mimetics."[23]

11. In June 2013, at a public meeting co-sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases and the National Cancer Institute, FDA reviewers shared some of their findings. B. Timothy Hummer, Ph.D., Supervisory Toxicologist, FDA Division of Metabolic and Endocrine Products, presented his conclusion that "[o]vert pancreatic toxicity or pancreatic neoplasms have not been observed across the [incretin-based] drug classes in [non-clinical testing] that would indicate a risk to human safety."[24] Solomon Iyasu, M.D., M.P.H., FDA Director, Office of Pharmacovigilance and Epidemiology, opined that existing adverse events data were insufficient to draw conclusions as to a cancer risk for incretin-based therapies.[25]

12. On February 27, 2014, FDA announced that its "comprehensive evaluation[]" was "now complete." In conjunction with the European Medicines Agency (EMA) and Dutch Medicines Evaluation Board, the Agency published its assessment of incretin-based therapies and the risk of pancreatic cancer in *NEJM*, the oldest peer-reviewed medical journal in the United States.[26] FDA employee co-authors were Amy G. Egan, M.D., M.P.H. (Deputy Director for Safety, Division of Metabolic and Endocrine Products, Center for Drug Evaluation and Research), Dr. Hummer, Ph.D., Todd Bourcier, Ph.D. (Supervisory Pharmacologist/Toxicologist,

---

[23] FDA, *FDA Drug Safety Communication: FDA Investigating Reports of Possible Increased Risk of Pancreatitis and Pre-Cancerous Findings of the Pancreas from Incretin Mimetic Drugs for Type 2 Diabetes* (Mar. 14, 2013) ("FDA Review Announcement") (attached as Ex. T to Laurendeau Decl.).

[24] B. Timothy Hummer, *FDA Surveillance of Adverse Drug Effects*, in NIDDK Workshop on Pancreatitis-Diabetes-Pancreatic Cancer Program Book, at 88 (2013) (attached as Ex. U to Laurendeau Decl.). Dr. Hummer is a co-author of the 2014 *NEJM* article.

[25] Solomon Iyasu, *FDA's Approach to Addressing a Pancreatic Safety Signal with Incretin Memetics*, in NIDDK Workshop on Pancreatitis-Diabetes-Pancreatic Cancer Program Book, at 90 (2013) (attached as Ex. V to Laurendeau Decl.).

[26] FDA/EMA Assessment (Ex. A) at 795.

Division of Metabolic and Endocrine Products), and Curtis Rosebraugh, M.D., Ph.D. (Director, Office of Drug Evaluation II).[27]

13. The *NEJM* publication was an official statement of FDA. The Agency's publication guidelines establish that an article or speech given by an FDA official is "FDA-Assigned," and thus represents the official position of the Agency, unless the article or speech contains a "disclaimer to emphasize that the views expressed in the article or speech do not necessarily represent the official views or policies of the agency."[28] The *NEJM* article did not contain such a disclaimer. The title is "Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment," and the source of the article is identified as "the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD."

14. The *NEJM* article describes the "comprehensive evaluations" independently conducted by FDA and EMA in 2013 and concludes:

> Thus, *the FDA* and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. *Both agencies agree that 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*. . . . *The FDA* and the EMA *believe that the current knowledge is adequately reflected in the product information or labeling* . . . .[29]

15. FDA again confirmed that it would not approve a pancreatic cancer labeling change for these therapies when it denied an April 19, 2012 petition by Public Citizen asking the Agency to remove Victoza from the market, based in part on the

---

[27] The article was "updated" (with no changes to the conclusions) on June 5, 2014. *See Corrections*, N. Engl. J. Med. 370:23 (June 5, 2014) (attached as Ex. W to Laurendeau Decl.).

[28] *See* FDA Staff Manual Guide 2126.3, Review of FDA-Related Articles and Speeches ("FDA Staff Manual") § 6.A (attached to Laurendeau Decl. as Ex. X).

[29] FDA/EMA Assessment (Ex. A) at 796 (emphasis added).

claim that Victoza increases the risk of pancreatic cancer. As support for its claim, Public Citizen relied on spontaneous adverse event reports of pancreatic cancer compiled in FDA's adverse event reporting database.

16. FDA rejected Public Citizen's use of adverse event data to draw conclusions about causation, explaining that the data "cannot be used to calculate the incidence of an adverse event in the U.S. population," in particular for events like pancreatic cancer that "occur[] commonly in the background untreated population and ha[ve] a long latency period."[30] The rejection letter further advised Public Citizen that the data cited by the Petition offered "no new evidence regarding the risk of pancreatic carcinoma . . . that would support *any changes to the current approved labeling*."[31]

17. FDA again considered the safety and efficacy of incretin-based therapies when it convened an Advisory Committee in 2014 to assess Saxenda (a higher dose of liraglutide (Victoza) for use in weight management). In a Briefing Book provided for the Committee, FDA said: "Risk for pancreatic cancer has more recently emerged as a concern with GLP-1-based therapies, including liraglutide. . . . However, animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association."[32] Referring to its February 2014 statement, FDA added: "Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, do not support pancreatic cancer as an incretin mimetic-mediated event."[33]

## THE LEGAL STANDARD FOR PREEMPTION

Federal preemption presents a pure question of law, and thus may be resolved on a motion for summary judgment. *See Indus. Truck Ass'n, Inc. v. Henry*, 125 F.3d 1305, 1309 (9th Cir. 1997); *Dalzin v. Belshe*, 993 F. Supp. 732, 734 (N.D. Cal. 1997)

---

[30] Public Citizen Letter (Ex. B) at 26, 36.
[31] *Id.* at 26, 37 (emphasis added).
[32] Saxenda Briefing Book (Ex. C) at 117.
[33] *Id.* at 313.

("It is axiomatic that questions of statutory interpretation [such as preemption] are questions of law" appropriately resolved through summary judgment).[34]

The Supremacy Clause "establishes that federal law 'shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.'" *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2577 (2011) (ellipsis in original) (quoting U.S. Const. art. VI, cl. 2). "Even where Congress has not completely displaced state regulation in a specific area," state law is preempted "to the extent that it actually conflicts with federal law." *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982). Such a conflict "arises when compliance with both federal and state regulations is a physical impossibility, or when state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.* (citations and internal quotation marks omitted). "Federal regulations" have just as much "pre-emptive effect [as] federal statutes." *Id.*

In product liability litigation involving prescription medications, federal law preempts state law failure-to-warn claims where there is "clear evidence" that FDA would "not have approved" the warning that a plaintiff alleges state law requires. *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).[35] In *Levine*, the inadequate warnings concerned Phenergan, an anti-nausea medication that can be administered intravenously by "IV push" (direct injection into the vein) or by "IV drip" (slow introduction of the medication, as diluted in a saline solution, from a hanging intravenous bag). If the medication enters the artery, it causes irreversible gangrene. Levine suffered gangrene—then amputation—resulting from an IV-push injection of

---

[34] Summary judgment is proper, of course, where 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).

[35] *See also, e.g.*, *Mensing*, 131 S. Ct. at 2581 n.8 (explaining that a drug manufacturer may establish a conflict between state and federal law, by "show[ing], by 'clear evidence,' that the FDA would have rescinded any change in the label [made through the CBE process] and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required").

Phenergan. Although the Wyeth labeling warned of the danger of gangrene and amputation from inadvertent intra-arterial injection, Levine alleged that the warning was inadequate because it failed to instruct doctors that they must use the IV-drip method. In response, Wyeth argued that the history of its communications with FDA demonstrated that the Agency would not have approved such a change in the labeling. The Supreme Court held that, "absent clear evidence that the FDA would not have approved" the proposed warning, there could be no federal preemption.[36]

The Supreme Court did not define the "clear evidence" standard in a formulaic phrase, but it did explain why the facts in *Levine* fell short of the standard. The Court found that, over twenty years, there were only sporadic communications between Wyeth and FDA and that FDA gave only "passing attention" to the issue. Wyeth and FDA only "intermittently corresponded about Phenergan's label."[37] In 1973 and 1976, Wyeth submitted supplemental new drug applications, with labeling changes, which FDA approved. But FDA did not act for seventeen years on Wyeth's third supplemental new drug application, submitted in 1981. In the interval, FDA in 1987 suggested different warnings about the risk of arterial exposure to Phenergan—and Wyeth submitted revised warnings incorporating those suggested changes in 1988—but the "FDA did not respond."[38] Eight years later, the Agency requested from Wyeth the labeling then in use, but still failed to address the company's 1981 or 1988 submissions. Only in 1998 did it approve the 1981 submission and instruct Wyeth that the final labeling must be identical to the approved package insert. This was two years before Levine's injury.

Based on this factual record, the trial court had "found 'no evidence . . . that either the FDA or the manufacturer gave more than passing attention to the issue of' IV-push versus IV-drip administration," and the Vermont Supreme Court had

---

[36] *Levine*, 555 U.S. at 571.
[37] *Id.* at 561, 563.
[38] *Id*. at 562.

concluded that "the FDA had not made an affirmative decision to preserve the IV-push method or intended to prohibit Wyeth from strengthening its warning about IV-push administration."[39] The Supreme Court itself observed that Wyeth did not argue that it supplied an "evaluation or analysis" of the alleged risks of the IV-push method, or that FDA had performed an evaluation or analysis of the scientific data.[40]

When the Supreme Court held that there was an absence of clear evidence that FDA would have rejected labeling advising against use of the IV-push method, it pointed specifically to the absence of evidence (i) that FDA addressed the specific issue of the relative risk of IV-push versus IV-drip administration of Phenergan, (ii) that FDA considered, or itself made, an evaluation of the scientific data, and (iii) that FDA made an affirmative decision not to authorize the proposed labeling change.

The same was true in *Gaeta v. Perrigo Pharmaceuticals Co*, 630 F.3d 1225 (9th Cir. 2011), *vacated on other grounds sub nom. L. Perrigo Co. v. Gaeta*, 132 S. Ct. 497 (2011). As in *Levine*, the Ninth Circuit in *Gaeta* "defined" what is clear evidence by explaining what did not satisfy that standard.[41] The plaintiffs alleged that the generic manufacturers of ibuprofen failed to warn of an increased risk of acute liver injury and renal failure when ibuprofen is taken concurrently with other medications known to be

---

[39] *Id*. at 572 (citation omitted).

[40] *Id*. at 572–73.

[41] In *Gaeta*, the Ninth Circuit held that state law failure-to-warn claims against *generic* manufacturers are not preempted, because (1) a generic manufacturer can utilize the CBE process to make changes to its labeling without prior approval by FDA, and (2) the generic manufacturer defendant in *Gaeta* had failed to show by "clear evidence" that FDA would not have approved the labeling change. 630 F.3d at 1235. The Supreme Court vacated the judgment in *Gaeta* in light of *Mensing*, which held that failure-to-warn claims against generic manufacturers *are* preempted. Because *Mensing* held that federal law categorically bars the generic manufacturer from changing the FDA-approved warnings, the Court did not have reason to reach the question whether "clear evidence" showed that FDA would have rejected the plaintiff's proposed warning. *See* 131 S. Ct. at 2581 n.8. Nothing in *Mensing*, however, affects *Gaeta*'s explanation of the "clear evidence" standard.

hepatotoxic. The defendant countered that this state-law, failure-to-warn claim was preempted, because FDA had considered and rejected the plaintiffs' proposed warning. The district court agreed with the defendant and granted summary judgment on preemption grounds.

On appeal, the Ninth Circuit accepted the premise that preemption is a viable defense in prescription drug cases: "In *Levine*, the Supreme Court left open the possibility that there could be preemption if a manufacturer was able to demonstrate, by *clear evidence*, that the FDA would not have approved the change to the drug's label proposed by the plaintiff."[42] For guidance as to what constitutes "clear evidence," the Ninth Circuit looked to the evidence found insufficient in *Levine*. Specifically, the court noted three central shortcomings in that evidence: (i) that the evidence reflected that FDA gave only "passing attention" to the precise issue of IV-push versus IV-drip, (ii) that FDA did not make or consider "an evaluation or analysis" of the risks at issue, and (iii) that FDA did not make a definitive decision, as it "apparently 'did not regard the proposed warning as substantively different' from the FDA-approved warning."[43]

The *Gaeta* court found these same shortcomings in the evidence provided by defendant Perrigo:

- First, although the Agency in earlier years had made a detailed review of the overall safety (including the risk of hepatotoxicity) of ibuprofen, "[n]owhere does [the defendant] point to any evidence that the FDA was presented with and actually considered the risk of hepatotoxicity due to concomitant use of ibuprofen and other drugs known to be hepatotoxic, which is the specific warning requested by the Gaetas in this case."[44]
- Second, the defendant offered no evidence that "it supplied the FDA with any

[42] *Gaeta v. Perrigo Pharm. Corp.*, 630 F.3d 1225, 1235 (9th Cir. 2011).
[43] *Id*. at 1236 (quoting *Levine*, 555 U.S. at 572 n.5).
[44] *Id*. at 1237.

'evaluation or analysis concerning the specific dangers' posed by such concomitant use."[45]

- Accordingly, third, the defendant offered no evidence that "the FDA refused to act" in light of such an evaluation and analysis.[46]

In determining whether "clear evidence" exists, this Court should begin by comparing the facts here with the facts of *Levine* and *Gaeta* and asking whether FDA would have rejected a pancreatic cancer labeling change given FDA's years-long attention to the issue of pancreatic cancer and its published conclusion that the labeling is adequate.

## ARGUMENT

### A. Plaintiffs' Failure-To-Warn Claims Are Preempted Under *Levine*.

***Did FDA focus on, and give attention to, the issue raised by Plaintiffs—whether there is a risk of pancreatic cancer that should be warned about in the labeling?*** The clear answer is yes. From at least September 2009, FDA was investigating the pancreatic safety of incretin-based medications, and in March 2013, FDA announced that it would conduct a comprehensive evaluation of a possible association between incretin-based medications and pancreatic cancer and that it would consider the entire body of scientific research and data available to date, as well as the Agency's own "further investigat[ion] [into the] potential pancreatic toxicity associated with the incretin mimetics."[47] In that March 2013 statement, FDA noted that it would "evaluate all available data to further understand this potential safety issue":

> The U.S. Food and Drug Administration (FDA) is evaluating unpublished new findings by a group of academic researchers [the Butler Group] that suggest an increased risk of pancreatitis, or inflammation of the pancreas, and pre-cancerous cellular changes called pancreatic duct metaplasia

[45] *Id*. (citation omitted).
[46] *Id*.
[47] FDA Review Announcement (Ex. T).

> in patients with type 2 diabetes treated with a class of drugs called incretin mimetics. . . . [T]he Agency intends to obtain and evaluate this new information. FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report. . . . *FDA is continuing to evaluate all available data to further understand this potential safety issue. In addition, FDA will participate in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute's (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013 to gather and share additional information*.[48]

***Did FDA conduct a serious, scientific review of the issue?*** Again, the clear answer is yes. The publication of "Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment" in February 2014 reflects the result of that evaluation—an evaluation that FDA describes as "comprehensive."[49] The Agency's years-long evaluation of a possible association between incretin-based therapies and pancreatic cancer included the following components:

- FDA performed its own independent pancreatic toxicology studies with Byetta, using three different rodent models of disease accompanied by a non-diseased control. Data from two models showed no drug-related pancreatic injury; from the third, "minimal-to-moderate" exacerbation of certain pancreatic background effects.[50]
- FDA "re-evaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals." These studies showed "no findings of overt pancreatic toxic effects." The Agency also found that "drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the

[48] *Id*. (emphasis added).
[49] FDA/EMA Assessment (Ex. A) at 795.
[50] *Id.* at 795-96.

level of human clinical exposure."[51]

- FDA required the manufacturers of incretin-based medications to conduct "3-month pancreatic toxicity studies in a rodent model of diabetes," which studies included "extensive" histopathological evaluation of the endocrine and exocrine pancreas. In those studies, "no treatment-related adverse effects on the pancreas were reported."[52]
- FDA subjected 120 pancreatic histopathology slides from one of these 3-month studies to "independent and blinded examination by three FDA pathologists," whose conclusions were "generally concordant" with the sponsors' conclusions.[53]
- FDA reviewed the safety data from more than 200 clinical trials, involving approximately 41,000 participants, more than 28,000 of whom used an incretin-based therapy. 15,000 of these participants used an incretin-based therapy for 24 weeks or more; 8,500, for 52 weeks or more.[54]
- FDA reviewed a manufacturer-sponsored pooled analysis of data from 14,611 patients with type-2 diabetes from 25 clinical trials in the Januvia/Janumet database and concluded that it "provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer."[55]
- FDA also examined safety data from two large, cardiovascular-outcome trials (the SAVOR and EXAMINE trials), which were conducted in patients with type-2 diabetes who were using two incretin-based therapies that are not a part of this MDL (Onglyza and Nesina).
    - The SAVOR trial was a randomized, double-blind, placebo-controlled trial involving 16,492 patients. The reported incidence of pancreatic

[51] *Id.* at 795.
[52] *Id.*
[53] *Id.*
[54] *Id.* at 796.
[55] *Id.*

cancer in SAVOR was: 5 in the group of patients treated with Onglyza versus 12 in the group of patients treated with placebo.[56]

- The EXAMINE trial was a randomized, double-blind, placebo-controlled trial involving 5,380 patients. There was no incidence of pancreatic cancer reported in either the Nesina or the placebo group.[57]

***Did FDA make an affirmative decision that the scientific evidence did not warrant a change in the labeling?*** Again, the clear answer is yes. It was on the basis of this years-long evaluation and analysis that FDA said that "assertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer, as expressed recently in the scientific literature and in the media, are *inconsistent* with the current data" and that "the current knowledge is *adequately* reflected in the product information or labeling."[58]

One month later FDA rejected a Public Citizen petition to withdraw Victoza from the market, noting that there was "no new evidence regarding the risk of pancreatic carcinoma . . . *that would support any changes to the current approved labeling*."[59] And later in 2014, having informed the Advisory Committee that "multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal . . . to date, do not support pancreatic cancer as an incretin mimetic-mediated event,"[60] FDA approved labeling for Saxenda that did not reference pancreatic cancer.

For these reasons, FDA's position regarding pancreatic cancer labeling is clear and specific to the issue raised in this litigation. Having (i) considered the very claim asserted by Plaintiffs in this litigation, and (ii) itself conducted a comprehensive evaluation of the scientific evidence concerning the alleged risk of pancreatic cancer, (iii) FDA concluded that the scientific data do not support labeling changes. There

---

[56] *Id.*
[57] *Id.*
[58] *Id*. (emphasis added).
[59] Public Citizen Letter (Ex. B) at 26 (emphasis added).
[60] Saxenda Briefing Book (Ex. C) at 313.

can be no clearer demonstration that FDA thoroughly considered the relevant safety issue and made a determination that the available data do not support including pancreatic cancer in the labeling.

FDA's years-long efforts in evaluating whether a pancreatic cancer risk is associated with use of incretin-based therapies reflects a level of attention and activity that is at the opposite end of the continuum from *Levine* and *Gaeta*. In *Levine*, FDA appeared to give only "passing attention" to the issues surrounding the relevant safety question, and the Agency's last word on the subject was two years before the plaintiff's injury. In *Gaeta*, FDA never addressed the issue of liver injury from concomitant use of ibuprofen and other hepatotoxic medications in any way, much less carried out an evaluation and analysis of the risks of concomitant use. Here, in contrast, FDA devoted several years to evaluation of the scientific record regarding the risk of pancreatic cancer before making an unprecedented and very public statement of its official conclusions. This investigation and statement constitute precisely the sort of "clear evidence" of FDA focus, analysis, and decision making contemplated by *Levine*.[61]

There is no question that these communications represent official FDA considerations and clear responses to the failure-to-warn allegations in this litigation.

---

[61] The facts here are similar to those in *Dobbs v. Wyeth Pharmaceuticals*, where the court found that FDA had given more than "passing attention" to the risk at issue and would have rejected the plaintiff's proposed warning. The court found specifically that (i) "despite its continuing review of [the drug] manufacturers' periodic reports of clinical trials and adverse events, the FDA continued to find no scientific evidence of a causal connection between [the drugs] and increased suicidality warranting an enhanced warning," (ii) rejected a series of citizen petitions, and (iii) for a series of supplemental New Drugs Applications "directed Wyeth to include the same language as appeared in the [original] label warnings regarding suicide." 797 F. Supp. 2d 1264, 1272–73 (W.D. Okla. 2011). The court found that FDA's attention to the issue continued even after the plaintiff's death, for the agency rejected an enhanced warning for pediatric users that Wyeth had unilaterally implemented. *Id.* at 1276.

Four of the February 27, 2014 *NEJM* article authors are FDA officials in the Center for Drug Evaluation and Research (including the Director of the Office of Drug Evaluation and the Deputy Director of the Division of Metabolic and Endocrine Products, Center for Drug Evaluation and Research); the title of the article reflects that it is an "FDA and EMA Assessment"; the article contains no disclaimer (indeed, it notes that it is "[f]rom the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration"); and the article is replete with statements about "FDA's" position on the issues. Likewise, the March 25, 2014 letter rejecting the April 2012 Public Citizen Petition related to Victoza plainly reflects an FDA-authorized investigation and response, authored by Janet Woodcock, M.D. (Director of FDA's Center for Drug Evaluation and Research). The September 2014 Briefing Book on Saxenda also reflects an FDA-authorized safety and efficacy review, authored by the Center for Drug Evaluation and Research, concluding that there was no reasonable evidence of a causal association. As it had done in the past in other contexts, FDA thereafter approved the Saxenda label without a reference to pancreatic cancer.[62]

At its core, Plaintiffs' position is that there cannot be "clear evidence" unless one or more of the Defendants actually proposed adding pancreatic cancer to its label and FDA rejected it. But that position must be wrong for at least three reasons.

*First*, the Supreme Court in *Levine* did not say that federal law preempts state

---

[62] Defendants submitted an expert report and a rebuttal report from Lawrence Goldkind, M.D. Currently Assistant Professor of Gastroenterology and Medicine and an attending physician at the Walter Reed National Military Medical Center, Dr. Goldkind worked at FDA from 1998 to 2003. He is the former Acting Division Director of the Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products. *See generally* Goldkind Rpt. (attached as Exhibit Y to Laurendeau Decl.); Goldkind Rebuttal Rpt. (attached as Exhibit Z to Laurendeau Decl.). Dr. Goldkind has also said that the *NEJM* article and FDA's response to the Public Citizen Petition related to Victoza each represents the official position of FDA. *See* Goldkind Rpt. at 8 (citing FDA Staff Manual).

law where there is "clear evidence" that FDA "*did* reject" the warning that state law requires. Rather, the Court said that federal law preempts where there is "clear evidence" that FDA "would not have approved" the labeling change that state law requires—a formulation that explicitly contemplates consideration of evidence regarding what FDA "would" have done had a manufacturer proposed a labeling change.

*Second*, as a matter of regulation, FDA will not approve a labeling change that is not supported by evidence of a causal association. But, if FDA has determined there is no such scientific evidence, then it would be inappropriate and pointless for a manufacturer to propose a labeling change to FDA. Thus, as Plaintiffs would have it, the case for preemption is weakest where the evidence is clearest that FDA would not approve a labeling change—i.e., where the manufacturer has no scientific basis even to propose such labeling change.

*Third*, contrary to principles of comity, Plaintiffs' position would mean that FDA's labeling determination lacks preemptive effect even when the Agency has taken unprecedented steps, first, to announce its intention to conduct a "comprehensive evaluation" of the scientific evidence relating to pancreatic cancer and, second, to publish its findings and conclusions, including its conclusion about the adequacy of the labeling. This position eviscerates *Levine*. And under such circumstances, it would be inappropriate (and illogical) for the manufacturer to propose a labeling change.[63]

---

[63] For purposes of preemption, it does not matter whether FDA's conclusion is the "right" one. The courts do not second-guess the Agency if it has given attention to the specific issue and studied and decided it. But it is noteworthy here that FDA's determination that the data do not support a causal association between incretin-based therapies and pancreatic cancer, reached after a thorough evaluation and analysis, reflects the scientific consensus of other regulatory bodies and professional associations, including the EMA, the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation (IDF). *See* European Medicines Agency, *Assessment Report for GLP-1*

**B. Plaintiffs Cannot Refute the Clear Evidence.**

Defendants first filed their motion for summary judgment based on preemption in April 2014. (Doc. No. 410). At that time, Plaintiffs claimed that they did not have sufficient evidence to oppose the motion. (Doc. No. 443). The Court denied Defendants' motion without prejudice and provided Plaintiffs the opportunity to pursue discovery regarding "what the [Food and Drug Administration] would or would not have done with respect to the proposed labeling change as expressed in *Wyeth v. Levine*." (Doc. Nos. 472 & 567, at 2:14-16).

Plaintiffs have completed their discovery and submitted an expert report from Dr. G. Alexander Fleming, who worked at FDA approximately three decades ago and is now Defendants' competitor.[64] Dr. Fleming did not identify any FDA statements or documents indicating that FDA would approve a pancreatic cancer labeling change for incretin-based therapies. To the contrary, at his deposition, Dr. Fleming conceded the facts material to this Motion. He testified:

- FDA has focused for years on the very question at issue in this litigation, i.e., whether the labeling for Defendants' drugs should include a pancreatic cancer warning;[65]
- FDA's Assessment is "unprecedented" and it came about because of "explosive assertions"[66] about the alleged risk of pancreatic cancer; and
- It was unusual for FDA to publish a statement that that the current labeling for a

---

*Based Therapies* (July 25, 2013) at 16 – 17 (Ex. AA to Laurendeau Decl.); ADA/EASD/IDF Statement (Ex. E).

[64] In addition to Dr. Fleming's report, Plaintiffs also submitted an expert report from David Madigan, Ph.D., which analyzed adverse event reports from FDA's database. *See* Madigan Rpt. at 3. Needless to say, this data is not unknown to FDA. FDA has repeatedly stated that adverse event reports are not relevant to assessing a causal association between pancreatic cancer and Defendants' drugs. *See, e.g.*, Public Citizen Letter (Ex. B) at 26.

[65] Fleming Tr. 122:23-123:1 (Ex. D).

[66] *Id.* at 95:20-96:6.

drug is adequate ("It's unusual in my experience, and I can't recall that being stated before.").[67]

Even more significantly, Dr. Fleming conceded that FDA has expressed its conclusion that the scientific evidence does not meet the regulatory standard for a labeling change:

- "Now, all we can get from Egan is that, in looking at everything, there are multiple streams of evidence. [FDA] haven't gotten to that threshold for FDA to mandate a change."
- "I think by definition, if [FDA] say that the label is adequate for now, that it hasn't reached that threshold [for changing the warnings section, i.e., 'reasonable evidence of a causal association'] for them."
- "I think we can just agree they [FDA] haven't reached that threshold [for changing the adverse reactions section of the label, i.e., "some basis to believe there is a causal relationship"].[68]
- "It's the official position that FDA is not mandating a change in the label."[69]

These concessions are dispositive. If FDA's official position is that the scientific evidence does not support a pancreatic cancer labeling change, then there is clear evidence FDA would reject the addition of such a labeling change if proposed by any of the defendant-manufacturers. That is so, because the regulatory standard for giving a warning or adding an adverse reaction—reasonable evidence of a causal association for a warning or some basis to believe there is a causal relationship for an adverse reaction—is the same whether it is FDA or the manufacturer which initiates the proposed warning.[70] Said differently, the evidence of causation must satisfy the

---

[67] *Id*. at 119:16-17.

[68] *Id*. at 153:6-154:3; *see also* 21 C.F.R. § 201.57(c)(6-7) (standards for warnings and adverse reactions sections of labeling).

[69] *Id.* at 234:14-15.

[70] *See* 21 C.F.R. § 201.57(c); Fleming Tr. at 223:11-224:05 (Ex. D). Dr. Fleming agrees with Defendants' expert Dr. Goldkind on this point. *See* Goldkind Rebuttal

same standard whether FDA *mandates* a labeling change or FDA *approves* a labeling change effectuated by CBE.

To be sure, Dr. Fleming said that FDA would accept a CBE that adds a pancreatic cancer warning.[71] But, in light of his concessions, accepting that assertion would require the Court to find that FDA would either disregard the regulatory standards or disown its own scientific findings. Neither is tenable, as Dr. Fleming ultimately agreed:

> Q. Do you agree with me that it would be absurd for the FDA to say, We've looked at all the data, we've done a comprehensive evaluation, we don't think there's any evidence of causal association, but go ahead and add a warning anyway?
>
> A. It would be a little absurd.[72]

## CONCLUSION

FDA has recognized that incretin-based therapies are an important treatment option for patients with type-2 diabetes. Thus, when assertions were made in the scientific literature and the media about a possible causal connection between the medications and pancreatic cancer, FDA acted in "unprecedented" fashion, launching its own comprehensive evaluation and reporting its findings, including its evaluation of the product labeling. FDA's well-considered conclusion—that no scientific basis exists to add pancreatic cancer to the labeling—is clear evidence that FDA would not have approved such a change.

---

Rpt. at 6 ("In assessing whether the science supports a change for the labeling with respect to pancreatic cancer, FDA employs the same standards to assess whether to *mandate* a label change and whether to *permit* a label change.").

[71] Fleming Tr. 73:3-5 (Ex. D).

[72] *Id.* at 201:21-202:1. *See also* Goldkind Rebuttal Rpt. at 13 ("FDA either makes a determination that cautionary language belongs in the labeling or FDA makes a determination that it does not belong.").

Dated: June 19, 2015

Respectfully submitted,

DOUGLAS R. MARVIN
F. LANE HEARD III
ANA C. REYES
PAUL E. BOEHM
WILLIAMS & CONNOLLY LLP

VICKIE E. TURNER
WILSON TURNER KOSMO LLP

By: s/ Vickie E. Turner
Vickie E. Turner
Attorneys for Defendant Merck Sharp & Dohme Corp.

LOREN H. BROWN
HEIDI LEVINE
RAYMOND WILLIAMS
DLA PIPER

By: s/ Loren H. Brown
Loren H. Brown
Attorneys for Defendant Novo Nordisk Inc.

RICHARD B. GOETZ
AMY J. LAURENDEAU
O'MELVENY & MYERS LLP

By: s/ Richard B. Goetz
Richard B. Goetz
Attorneys for Defendant Amylin Pharmaceuticals, LLC

NINA M. GUSSACK
ALINE FAIRWEATHER
KENNETH J. KING
PEPPER HAMILTON LLP

By: s/ Kenneth J. King
Kenneth J. King
Attorneys for Defendant
Eli Lilly and Company, a
Corporation

**SIGNATURE ATTESTATION**

Pursuant to Section 2.f.4 of the Court's CM/ECF Administrative Policies, I hereby certify that authorization for the filing of this document has been obtained from each of the other signatories shown above and that all signatories have authorized placement of their electronic signature on this document.

By: s/ Vickie E. Turner
Vickie E. Turner