UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF LOUISIANA

In re Actos (Pioglitazone) Product Liability Litigation	* * *	6:11-md-2299
This Document Relates to: *Terrence and Susan Allen v. Takeda Pharmaceuticals International, Inc., et al.*, No. 6:12-cv-0064-RFD-PJH	* * * * *	JUDGE DOHERTY MAGISTRATE JUDGE HANNA

DEFENDANTS' RULE 50(b) MOTION FOR FOR JUDGMENT AS A MATTER OF LAW

May It Please The Court:

Defendants Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals International, Inc., Takeda Pharmaceuticals LLC, Takeda Development Center Americas, Inc., Takeda California, Inc. (collectively, "Takeda"), and Eli Lilly and Company ("Eli Lilly") (collectively with Takeda, "Defendants"), respectfully move this Court, pursuant to Fed. R. Civ. P. 50(b), for judgment as a matter of law on all of Plaintiffs' claims and on Plaintiffs' demand for punitive damages. As grounds for this Motion, Defendants state:

- Federal law preempts all of Plaintiffs' claims against Lilly because federal law did not permit Lilly to change the Actos label.
- Federal law preempts all of Plaintiffs' claims against Takeda and Lilly for multiple reasons.
- All of Plaintiffs' claims fail as a matter of law because Plaintiffs did not offer sufficient evidence to meet their burden on the issue of specific causation.
- Plaintiffs' breach of implied warranty claim against Takeda also fails as a matter of law because Plaintiffs did not present evidence that Actos is unfit for its intended purpose or is not minimally safe.

- Plaintiffs' demand for punitive damages fails as a matter of law because Plaintiffs did not show that Defendants engaged in a wanton disregard of safety.

- Plaintiffs' demand for punitive damages against Lilly fails for several additional reasons.

Further support and grounds for this Motion are set forth in the accompanying Memorandum of Law in Support of Defendants' Rule 50(b) Motion for Judgment as a Matter of Law, and exhibits thereto,[1] which are incorporated herein by reference.

WHEREFORE, Defendants respectfully pray that this Motion be granted in Defendants' favor as to each of Plaintiffs' claims and on Plaintiffs' demand for punitive damages.

DATED: June 27, 2014

Respectfully Submitted,

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[1] Defendants are submitting an omnibus set of exhibits in support of their Rule 50(b) motion and their Rule 59 motion.

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CERTIFICATE OF SERVICE

I hereby certify that on June 27, 2014, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system, which will send a notice of electronic filing to Plaintiffs' Steering Committee, Lead Defense Counsel and Defendants' and Plaintiffs' designees. The designees will forward the NEFs to the appropriate attorneys as outlined by the Court's Case Management Order: Notice of Procedure [D.E. 3398].

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MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' RULE 50(b) MOTION FOR JUDGMENT AS A MATTER OF LAW

May It Please The Court:

Defendants Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals International, Inc., Takeda Pharmaceuticals LLC, Takeda Development Center Americas, Inc., Takeda California, Inc. (collectively, "Takeda"), and Eli Lilly and Company ("Eli Lilly") (collectively with Takeda, "Defendants"), respectfully submit this Memorandum of Law in Support of Their Rule 50(b) Motion for Judgment as a Matter of Law.

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INTRODUCTION

At trial, Plaintiffs alleged that Terrance Allen's use of ACTOS® ("Actos") to treat his type 2 diabetes caused him to develop bladder cancer. Plaintiffs did not allege that it was wrong for Defendants to market Actos. To the contrary, they told the jury that diabetes is a "horrific" and "nasty, nasty, deadly disease," and that Actos should stay on the market. For similar reasons, Mr. Allen's own physicians continue to prescribe Actos to some of their patients. Indeed, the undisputed evidence presented at trial showed that Actos is an effective medicine for controlling blood sugar in type 2 diabetics, and that Defendants' marketing of the drug has been socially beneficial, saving and improving the quality of countless lives.

Nonetheless, Plaintiffs sued, alleging that Defendants failed to adequately warn Mr. Allen's prescribing physicians about a potential "low" risk of bladder cancer from Actos. Plaintiffs made that allegation even though Actos' FDA-approved labeling has always contained information about bladder cancer – including human bladder cancer data added to the Actos label's Precautions section at the direction of the FDA four and a half years before Mr. Allen was diagnosed. Plaintiffs argued that Defendants' alleged failure to warn was not merely negligent, but that it also met New York's "strict" standard for punitive damages – a "wanton disregard" for the "safety of others," implying "a criminal indifference to civil obligations."

The jury accepted all of Plaintiffs' allegations, and awarded Plaintiffs $1.475 million in compensatory damages and $9 billion in punitive damages – reported to be the seventh largest punitive damages verdict in U.S. history. If sustained, the verdict would send an unmistakable warning to all pharmaceutical manufacturers that they may well be litigated out of business for marketing life-saving drugs with a "low" potential risk of adverse effects even when that risk is disclosed with the express approval of the FDA. Neither the compensatory nor the punitive

verdicts can stand. For the following reasons, Defendants are entitled to judgment as a matter of law on all of Plaintiffs' claims and on Plaintiffs' demand for punitive damages.

- Federal law preempts all of Plaintiffs' claims against Lilly because federal law did not permit Lilly to change the Actos label.
- Federal law preempts all of Plaintiffs' claims against Takeda and Lilly for multiple reasons.
- All of Plaintiffs' claims fail as a matter of law because Plaintiffs did not offer sufficient evidence to meet their burden on the issue of specific causation.
- Plaintiffs' breach of implied warranty claim against Takeda also fails as a matter of law because Plaintiffs did not present evidence that Actos is unfit for its intended purpose or is not minimally safe.
- Plaintiffs' demand for punitive damages fails as a matter of law because Plaintiffs did not show that Defendants engaged in a wanton disregard of safety.

STANDARD

A Rule 50 motion for judgment as a matter of law should be granted if "a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for the party on that issue." Fed. R. Civ. P. 50. In order to defeat a Rule 50 motion, "the nonmovant must present 'substantial evidence opposed to the motion.'" *Viazis v. American Ass'n of Orthodontists*, 314 F.3d 758, 761 (5th Cir. 2002) (internal citation and quotations omitted). This standard applies even when the court is exercising diversity jurisdiction. *See, e.g., Dawson v. Wal-Mart Stores, Inc.*, 978 F.2d 205, 208 (5th Cir. 1992) (noting that in diversity cases "the sufficiency or insufficiency of the evidence in relation to the verdict is governed by a federal standard"). When deciding a Rule 50 motion, the "court should consider all of the evidence – not just that evidence which supports the non-mover's case – but in the light and with all reasonable inferences most favorable to the party

opposed to the motion." *Goodner v. Hyundai Motor Co., Ltd.*, 650 F.3d 1034, 1040 (5th Cir. 2011).

ARGUMENT

1. Federal law preempts all of Plaintiffs' claims against Lilly because federal law did not permit Lilly to change the Actos label.[1]

Lilly helped to promote a socially beneficial medicine that is used to treat a "nasty, deadly disease" and that Mr. Allen's physicians continue to prescribe. Lilly marketed the drug with an FDA-approved label, which Lilly was not permitted to change.

Even though the FDA approved the label, Plaintiffs called Dr. David Kessler to testify that the Actos label did not adequately warn about a potential risk of bladder cancer while Mr. Allen was taking Actos. According to Dr. Kessler, bladder cancer should have been added to the Warnings section of the Actos label via the FDA's changes being effected ("CBE") process in January 2004. (Ex. 26, Vol. VIII, 02/11/14 Tr. at 1014:7-9, 1015:8-12, 1019:10-21).[2] But, it is undisputed that Lilly has never been the holder of the new drug application ("NDA") for Actos.[3] And, as another pharmaceutical MDL court has noted, only the NDA holder has the authority to change a prescription drug label via the CBE process. *See In re Fosamax (Alendronate Sodium)*

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[1] Plaintiffs asserted two claims against Lilly – failure to warn and "negligent marketing." But, the Plaintiffs' negligent marketing claim turned out to be nothing more than their failure to warn claim by a different name. (*See, e.g.*, Ex. 24, Vol. V, 02/06/14 Tr. 666:25 – 667:3 (Plaintiffs' counsel describing "failure to warn" as the "underlying tort behavior that's the basis of this case"); Ex. 38, Vol. XXXV, 04/02/14 Tr. at 5828:5-7 (Plaintiffs opposing Rule 50(a) motion on the negligent marketing claim by arguing that Defendants "could have warned by 2004.")). Other than warnings, Plaintiffs pointed to no aspect of Defendants' "marketing" of Actos that was an alleged proximate cause of Mr. Allen's injury.

[2] The CBE process is spelled out in the FDA regulations governing prescription drug labeling. *See* 21 C.F.R. § 201.57(c)(6) (2006) (stating, in pertinent part: "In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established."); 21 C.F.R. § 314.70(c)(6)(iii)(A) (2006) (permitting "holder of an approved application" to "strengthen a contraindication, warning, precaution, or adverse reaction" in the label without obtaining prior FDA approval for the change).

[3] (*See* Ex. 3, 12/14/98 Agreement Between Lilly and Takeda, P470).

Prods. Liab. Litig. (No. II), 2012 WL 181411, at *3 (D.N.J. Jan. 17, 2012) (stating that a distributor of a name-brand drug "has no power to change [the drug's] labeling" because "[t]hat power lies with the applicant who filed the New Drug Application (NDA) seeking approval to market [the drug]") (citing 21 U.S.C. § 355(b); 21 C.F.R. § 314.70). (*See also* Ex. 37, Vol. XXXII, 03/28/14 Tr. at 5134:13-25, 5280:12 – 5281:10 (undisputed testimony by Defendants' regulatory expert, Dr. Feigal, that the NDA holder is the only company that can initiate a label change)).

Indeed, during closing argument, Plaintiffs' counsel conceded that "Lilly can't go in and change the label." (Ex. 40, Vol. XXXVII, 04/07/14 Tr. at 6247:15). Plaintiffs' counsel was forced into that concession because Dr. Kessler testified that he did not have an opinion on whether Lilly had the responsibility to add bladder cancer to the Warnings section of the Actos label.

> Q. I have one question about, about labeling. And, we'll get into labeling more in a little bit. But I think you testified earlier in response to questions from Mr. Lanier that the company, the manufacturer of the drug is responsible for its label. Is that right?
>
> A. Of course.
>
> Q. And that's Takeda, right?
>
> A. I'd leave it to others. You have Takeda, Lilly, arrangements and others can opine on that.
>
> Q. You're not expressing an opinion that Lilly, who was not the holder of the NDA, had a responsibility to change the label, are you?
>
> A. I'm not expressing – I have issued no opinion with regard to that.
>
> Q. You have no opinions with respect to Lilly and the labeling, right?

> A. I'd have to go back and look at my report, but I don't believe I have opinions specifically with regard to Lilly, but I'd have to check that.

(Ex. 27, Vol. IX, 02/12/14 Tr. at 1191:8 – 1192:1).

Because federal law would not permit Lilly to make any change to the FDA-approved Actos label, Plaintiffs' claims against Lilly are preempted under the doctrine of federal conflict preemption. In *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2577-78 (2011), the Supreme Court ruled that federal law preempts failure to warn claims against generic drug manufacturers because generic drug manufacturers may not make a CBE change to their labels if that change makes the label different than the FDA-approved label of the name brand counterpart. Similarly, in the Fosamax MDL, the court ruled that the Supreme Court's rationale in *Mensing* precludes failure to warn claims against a company that distributes or markets a name brand drug if that company is not the NDA holder for that drug.

In the Fosamax MDL, a group of plaintiffs (the "*Welch* plaintiffs") brought claims against Watson Pharmaceuticals ("Watson"), alleging that Watson was both a manufacturer of generic Fosamax (alendronate) and a distributor and marketer of name brand Fosamax. *See In re Fosamax*, 2012 WL 181411, at *1 (noting plaintiffs alleged that Watson was an "authorized distributor of branded Fosamax" and that "under the agreement between Merck and Watson, Merck manufactured and supplied alendronate and Watson marketed and sold the drug under branded name Fosamax"). The Fosamax MDL court held that all claims against Watson were preempted under *Mensing*:

> As a result of the scheme set forth by the FDCA, Watson has no authority to initiate a labeling change of Fosamax. That authority lies with the FDA and/or with Merck. Even taking the allegation in *Welch* as true, a contractual relationship between Watson and Merck cannot change the fact that Watson is not the NDA holder. Consequently, Watson has no power to unilaterally change

> Fosamax labeling. Because Watson could not "independently do under federal law what state law [allegedly] requires of it," the state law claims brought against it are preempted. *Mensing*, 131 S. Ct. at 2579.

Id. at *3-4. The court therefore dismissed the plaintiffs' claims against Watson regardless of whether the plaintiffs used generic or branded Fosamax.[4]

The Fosamax MDL court's reasoning is unassailable. A company that distributes or promotes a name brand prescription drug, but that is not the NDA holder for that drug, is no more able to change a drug's FDA-approved labeling than is a manufacturer of the generic version of the drug. Plaintiffs can point to no federal statute or regulation that would permit a non-NDA holding co-promoter, such as Lilly, to change Actos' FDA-approved labeling. Therefore, federal law preempts Plaintiffs' claims against Lilly.

Plaintiffs cannot defeat preemption by arguing that Lilly could have issued a "Dear Doctor letter" about bladder cancer or added a Warning about bladder cancer to the written materials (brochures, *etc.*) that its sales representatives provided to physicians. As the Supreme Court noted in *Mensing*, because Dear Doctor letters qualify as "labeling" under FDA regulations, a "Dear Doctor letter that contained substantial new warning information would not be consistent with the drug's approved labeling." 131 S. Ct. at 2576. And, as this Court has noted, all written materials distributed by pharmaceutical sales representatives qualify as "labeling" under FDA regulations. *See In re Actos (Pioglitazone) Prods. Liab. Litig.*, 2014 WL 46579, at *7 (W.D. La. Jan. 6, 2014) (citing 21 CFR § 202.1(I)(2))).

Nor can Plaintiffs save their claims by asserting that Lilly made representations or concealed material facts outside of the context of the labeling for Actos. Plaintiffs presented no

[4] The Third Circuit recently affirmed the Fosamax MDL court's dismissal of all of the *Welch* plaintiffs' claims against non-NDA holders, including their claims against Watson. *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 751 F.3d 150 (3d Cir. 2014).

evidence concerning representations made by Lilly sales representatives to Mr. Allen's prescribing physicians, much less evidence that their representations were inconsistent with the FDA-approved label. In any event, any claim of liability based on Lilly's marketing of Actos fails based on insufficient evidence of causation. Plaintiffs presented no evidence of any actual communication between a Lilly sales representative and Mr. Allen's prescribing physicians during the relevant time period. Specifically:

- Plaintiffs' warning expert, Dr. Kessler, testified that additional data about bladder cancer should have been added to the Actos label in January 2004. (Ex. 26, Vol. VIII, 02/11/14 Tr. at 1014:7-9, 1015:8-12, 1019:13-18). Thus, pre-2004 interactions between Lilly representatives and Mr. Allen's physicians cannot support Plaintiffs' claims against Lilly.

- Dr. Reilly first prescribed Actos to Mr. Allen in April 2006. (Ex. 45, Dr. Reilly Testimony, P7512A at 14:20 – 15:5). Sales call records show only three sales calls by Lilly representatives on Dr. Reilly's office in 2004, and none at all thereafter. (Ex. 49, Spreadsheet List of Lilly and Takeda Sales Representative Visits to Dr. Reilly's Office, P7153 at 28, 34, 36). Dr. Reilly testified that merely because a Lilly sales representative appeared at his office does not mean that Dr. Reilly actually spoke with the representative. (Ex. 45, Dr. Reilly Testimony, P7512A at 29:13 – 30:6).

- Dr. Lamb's first contact with Mr. Allen was in December 2007. (Ex. 46, Dr. Lamb Testimony, P7514A at 12:3-7). Sales call records show only three sales calls by Lilly representatives in 2004, and none thereafter. (Ex. 48, Spreadsheet List of Lilly and Takeda Sales Representative Visits to Dr. Lamb's Office, P7135 at 7). Dr. Lamb could not recall whether any Lilly sales representatives ever met with her regarding Actos. (Ex. 46, Dr. Lamb Testimony, P7514A at 55:9-24).

This evidence is insufficient to support a finding that Lilly's alleged failure to warn of bladder cancer "caused" Drs. Reilly and Lamb to prescribe Actos to Mr. Allen.

Plaintiffs also cannot defeat preemption by arguing that Lilly could have asked the FDA to urge Takeda to add bladder cancer to the Warnings section of the label and that such an effort might have been successful. The Supreme Court rejected a similar argument in *Mensing*. The plaintiffs in *Mensing* argued that their claims were not preempted because the generic manufacturers could have asked the FDA to try and negotiate a new label with the name brand

manufacturer and it was "possible" that FDA would have honored the request and negotiated a new label. *Mensing*, 131 S. Ct. at 2578-79. The Supreme Court rejected this argument as a matter of law because it would permit parties to defeat conflict preemption through pure conjecture and thus render the doctrine of conflict preemption meaningless:

> If these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes, it is unclear when, outside of express pre-emption, the Supremacy Clause would have any force. We do not read the Supremacy Clause to permit an approach to pre-emption that renders conflict pre-emption all but meaningless.

Id. at 2579.

Finally, Plaintiffs cannot defeat preemption by arguing that Lilly could have simply stopped co-promoting Actos in January 2004 (the time that Dr. Kessler says the label should have been changed). The Supreme Court has also rejected such a "stop-selling" argument:

> The Court of Appeals reasoned that [the generic manufacturer] could escape the impossibility of complying with both its federal- and state-law duties by "choos[ing] not to make [sulindac] at all." [*Mutual Pharm. Co. v. Bartlett*,] 678 F.3d [30], at 37 [(1st Cir. 2012)]. We reject this "stop-selling" rationale as incompatible with our pre-emption jurisprudence. Our pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability. Indeed, if the option of ceasing to act defeated a claim of impossibility, impossibility pre-emption would be "all but meaningless."

Mutual Pharm. Co. v. Bartlett, 133 S. Ct. 2466, 2477 (2013) (quoting *Mensing*). *See also Morris v. PLIVA, Inc.*, 713 F.3d 774, 778 (5th Cir. 2013) (federal law preempted any claim that drug manufacturer "should have ceased manufacturing [its] products because of insufficient warnings" because such a claim "conflicts with the FDA's exclusive authority to approve drugs and drug labels"). Thus, upholding liability against Lilly would not only discourage

pharmaceutical companies from marketing socially beneficial drugs, but also it would conflict with well-established preemption precedent.

2. Federal law preempts all of Plaintiffs' claims against Takeda and Lilly for multiple reasons.[5]

The Constitution's Supremacy Clause also bars Plaintiffs' claims more broadly. Plaintiffs' state law theory of liability at trial was simple: Takeda should have added bladder cancer to the Warnings section of the Actos label in January 2004.[6] Disclaiming any reliance on the rest of the label, Plaintiffs told the jury that bladder cancer information "buried somewhere else" was inadequate. (Ex. 40, Vol. XXXVII, 04/07/14 Tr. at 6162:9-6163:12 (closing argument)). But Plaintiffs' theory of liability conflicts with federal law for the following reasons.

First, there is "clear evidence" that the FDA would not have allowed Takeda to add bladder cancer to the Warnings section of the label before Mr. Allen's injury occurred. *See Wyeth v. Levine*, 555 U.S. 555, 571 (2009) (stating that a plaintiff's failure to warn claim against drug manufacturer would be preempted under the doctrine of impossibility preemption if there is "clear evidence that the FDA would not have approved a change to [the drug's] label"). Unlike

[5] Plaintiffs asserted failure to warn and "negligent marketing" claims against Lilly and Takeda, and a breach of implied warranty claim against Takeda. But, all of those claims turned out to be based on nothing more than allegations of failure to provide adequate warnings. As is noted above, Plaintiffs described "failure to warn" as the "underlying tort behavior that's the basis of this case," (Ex. 24, Vol. V, 02/06/14 Tr. 666:25 – 667:3), Plaintiffs opposed Defendants' Rule 50(a) motion on the negligent marketing claim by arguing that Defendants "could have warned by 2004," (*see* Ex. 38, Vol. XXXV, 04/02/14 Tr. at 5828:5-7), and other than warnings, Plaintiffs pointed to no aspect of Defendants' "marketing" of Actos that was an alleged proximate cause of Mr. Allen's injury. And, the Court instructed the jury that Plaintiffs' breach of implied warranty claim against Takeda was based on Plaintiffs' allegation that "Actos is not fit for its ordinary purpose because Actos can cause bladder cancer and because Takeda *did not adequately warn* the medical community of this potential danger." (Ex. 41, Written Jury Instructions at 14) (emphasis added).

[6] Plaintiffs' counsel expressly disclaimed arguments that a Warning should have been added earlier, stating: "I don't know that any of us are contending that December '02 should have been a warning. I certainly am not suggesting that." (Ex. 37, Vol. XXXII, 03/28/14 Tr. at 5236:13-16 (Plaintiffs' counsel cross-examining Dr. Feigal)).

Wyeth, where there was "no evidence in this record that either the FDA or the manufacturer gave more than passing attention to the [risk at] issue," here the evidence shows that FDA and Takeda were actively evaluating the bladder cancer risks and calibrating the required warnings statements during the period at issue. *Id.* at 572. In 2006, the FDA directed that bladder cancer go in the Precautions section after the FDA had reviewed data from Actos clinical trials (including PROactive) and the first interim KPNC analysis.[7] By 2009, the FDA had received additional data, including the second interim KPNC analysis.[8] In May 2009, the FDA approved ACTOplus met XR, with bladder cancer referenced in the Precautions section of the label and a reference to bladder cancer in the Medication Guide (which is written for patients, but which is also included as part of the text of the label); the FDA added bladder cancer to the Actos Medication Guide a few months later.[9]

Further, in 2011, after completing its review of the third interim (5-year) analysis from the KPNC study – an ongoing, 10-year epidemiological study of bladder cancer in Actos patients – the FDA directed that bladder cancer (including the KPNC data) be placed in the "Warnings

[7] (*See* Ex. 9, 08/31/05 Takeda submission of bladder cancer data to FDA, D1501; Ex. 10, 06/01/06 Takeda submission of bladder cancer data to FDA, D1584; Ex. 11, 06/19/06 Contact Report Form, D1591 (summarizing telephone call from FDA's Dr. Robert Misbin during which Dr. Misbin stated that a label change regarding bladder cancer was needed, but that he was "not implying to advance language into a warning or precaution"); Ex. 12, 07/28/06 FDA Approval Package for Duetact (a product containing Actos), D1621 at 4, 25-26, 45-46, 53-64, 170-74 (stating that Actos human clinical trial data regarding bladder cancer should be added to the Precautions section after that section's discussion of rat bladder cancer data); Ex. 37, Vol. XXXII, 03/28/14 Tr. 5160:14 – 5162:25 (Feigal); Ex. 13, 08/30/06 letter from FDA to Takeda, D1639 at 1 and 18 (approving the addition of Actos human clinical trial data regarding bladder cancer to the Precautions section of the Actos label)).

[8] (*See* Ex. 16, 01/25/10 letter from Takeda to the FDA, D1943 at 1 (noting that Takeda submitted the second interim KPNC analysis to the FDA in August 2007)).

[9] *See In re Actos (Pioglitazone) Prods. Liab. Litig.*, 2011 WL 60298, at *2 and *2 n.11 (W.D. La. Jan. 7, 2014) (summarizing undisputed regulatory and labeling history of products containing Actos). (*See also* Ex. 15, 09/09/09 letter from the FDA to Takeda, D1916 at 1 and 7).

and Precautions" section of the Actos label.[10] Prior to 2011, before the FDA had completed its review of the third interim KPNC analysis and before the Actos label was converted to the "PLR" format, the FDA had repeatedly determined that bladder cancer should go in the Precautions section rather than the Warnings section after reviewing the then-available data.[11] The FDA's course of action from 2006 to 2011 is "clear evidence" that FDA would not have approved putting bladder cancer in the Warnings section before Mr. Allen suffered his injury.[12]

Second, to the extent that the Plaintiffs' theory of liability is that the FDA "got it wrong," the Plaintiffs' theory conflicts with the FDA's exclusive authority to determine that a drug is safe and effective as labeled on the date of approval. States (and jurors applying state law) are not

[10] (*See* Ex. 16, 01/25/10 letter from Takeda to the FDA, D1943 at 1-2 (submitting the third interim (5-year) analysis of KPNC to the FDA); Ex. 17, 09/17/10 FDA Drug Safety Communication: Ongoing Safety Review of Actos (pioglitazone) and Potential Increased Risk of Bladder Cancer After Two Years Exposure, D1977 at 1 (stating that FDA "is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether Actos (pioglitazone), is associated with an increased risk of bladder cancer"); *id.* at 3 (stating that the FDA would "complete" its review "in several months"); Ex. 19, 07/11 Actos Label, P2456 at 6 (discussing the 5-year interim analysis of KPNC)).

[11] As Defendants' regulatory expert, Dr. Feigal, explained, the FDA's new "PLR" format combined the Warnings section and the Precautions section into a single "Warnings and Precautions" section. The FDA provided a timetable for manufacturers to convert their products' labels to the new "PLR" format, and the FDA approved the conversion of the Actos label to the "PLR" format in 2011, after Mr. Allen developed bladder cancer. (Ex. 37, Vol. XXXII, 03/28/14 Tr. at 5138:10 – 5140:7, 5200:25 – 5201:4 (Feigal)). The labels for other Actos-containing products remained in the old format in 2011, so the KPNC data was put into the Precautions section of the labels for those products at that time. *See In re Actos Prods. Liab. Litig.*, 2014 WL 60298, at *2 (W.D. La. Jan. 7, 2014).

[12] Plaintiffs will note that in 2011 Takeda also provided the FDA with a meta-analysis of the bladder cancer data from all of the Actos clinical trials. However, as is discussed in more detail in section 5 below, Plaintiffs' argument about the 2011 meta-analysis is a red herring because the meta-analysis did not prompt the FDA's 2011 labeling action. Takeda performed the meta-analysis at the request of European regulators, not the FDA. In 2011, the FDA directed Takeda to add the KPNC data, not the meta-analysis, to the label. The meta-analysis adds nothing to the equation, and the FDA has never directed Takeda to add the meta-analysis to the label. In 2006, the FDA conducted a combined analysis of the bladder cancer data from the two longest Actos clinical trials (two 3-year trials) and found a statistically significant difference between the number of bladder cancer cases in Actos patients and the number of bladder cancer cases in non-Actos patients. That combined analysis drove the FDA's 2006 labeling decision. The 2011 meta-analysis found only five additional bladder cancer cases (3 in patients taking Actos and 2 in patients not taking Actos), and although it also found a statistically significant difference between Actos patients and non-Actos patients, that difference was smaller than the difference seen in the FDA's 2006 combined analysis of the two longest Actos clinical trials.

empowered to make that determination. And to do so would be in direct contravention of the Supremacy Clause. *See, e.g., Bartlett*, 133 S. Ct. at 2473 ("[I]t has long been settled that state laws that conflict with federal law are without effect.") (internal quotation marks omitted). While the FDA's initial approval of Actos occurred in 1999, it is undisputed that the FDA also approved NDAs for products containing Actos in 2005 (ACTOplus met), 2006 (Duetact), and 2009 (ACTOplus met XR), and each of those FDA actions included approval of labels with bladder cancer in the Precautions section.[13] Each of those approvals constituted a finding by the FDA that on the date of approval the products were safe and effective under the FDA-approved labeling.[14] Each of those approvals thus overrides any state-law theory that *as of that date* bladder cancer should have been in the Warnings section of the label because Congress placed the approval of a new drug's safety and efficacy as labeled solely in the hands of FDA, not with juries.[15]

Third, Plaintiffs' claims are barred by the doctrine of obstacle preemption, a version of conflict preemption. *See Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000) (stating that obstacle preemption occurs where a state law claim "stands as an obstacle to the accomplishment . . . of the full purposes and objectives of Congress."). The evidence presented at trial showed that the FDA has always paid close attention to the potential risk of bladder

[13] *See In re Actos (Pioglitazone) Prods. Liab. Litig.*, 2014 WL 60298, at *2 & *2 n.11 (summarizing undisputed regulatory and labeling history of products containing Actos).

[14] *See* 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d) (1999-2013); *see also* 21 C.F.R. § 314.105(c) (1999-2013) (mandating that FDA "is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards"); Ex. 29, Vol. XI, 02/14/14 Tr. at 1481:2-14 (Dr. Kessler testifying to the FDA's involvement in determining labeling content during the approval process).

[15] In 2009, the FDA directed Takeda to add bladder cancer to the Actos Medication Guide. (Ex. 15, 09/09/09 letter from the FDA to Takeda, D1916 at 1 and 7). Once a discussion of bladder cancer was added to the Medication Guide, federal law prohibited Takeda from changing the label's discussion of bladder cancer via a CBE. *See* 21 C.F.R. §§ 208.20(a)(2) (2008), 314.70(b)(2)(v)(B) (2008). *See generally, Mensing*, 131 S. Ct. 2567.

cancer from Actos, and used its expert judgment in determining when labeling changes should be made and the language that should be used for those labeling changes. In short, Plaintiffs' claims interfere with the purposes and objectives of the FDA regulatory scheme and are therefore preempted.[16] Billions of dollars in liability should not be imposed on companies that market prescription drugs consistent with FDA-approved labels that the companies could not have changed.

3. All of Plaintiffs' claims fail as a matter of law because Plaintiffs did not offer sufficient evidence to meet their burden on the issue of specific causation.

Compounding the infirmities with the unprecedented verdict, Plaintiffs failed to offer sufficient evidence of specific causation. Dr. Delacroix was the only witness to testify that Actos was the cause of Mr. Allen's bladder cancer. (*See* Ex. 32, Vol. XVIII, 02/27/14 Tr. 2528:22-23 ("But for the use of Actos, I don't believe Terry Allen would have gotten bladder cancer.") (Delacroix)). However, a "claim cannot stand or fall on the mere *ipse dixit* of a credentialed witness." *Guile v. United States*, 422 F.3d 221, 227 (5th Cir. 2005) (internal citation and quotation omitted). Instead, an "expert's opinion must be supported to provide substantial evidence" because "if an opinion is fundamentally unsupported, then it offers no expert assistance to the jury." *Id.* (internal citations and quotations omitted). *See also Wackman v. Rubsamen*, 602 F.3d 391, 400 (5th Cir. 2010) ("In reviewing challenges to expert testimony in the sufficiency [of evidence] context, federal courts must be mindful that evidence sufficient to support a jury verdict must be *substantial* evidence.") (quoting *Guile*, 422 F.3d at 226);

[16] Plaintiffs cannot avoid preemption by arguing that Takeda misrepresented or failed to disclose information to FDA. Both the Supreme Court and the Fifth Circuit have held that such arguments inappropriately invade FDA's territory in policing manufacturers who violate its regulations, and this case presents precisely the scenarios *Buckman* and *Lofton* sought to avoid. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001); *Lofton v. McNeil Consumer & Specialty Pharm.*, 672 F.3d 372, 380 (5th Cir. 2012); *see also* 21 C.F.R. § 314.105(c) ("FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide."); 21 U.S.C. § 337(a).

Genmoora Corp. v. Moore Bus. Forms, Inc., 939 F.2d 1149, 1163 (5th Cir. 1991) ("An expert's testimony is not substantial if it is based merely on speculation and conjecture without basis in fact.").

Dr. Delacroix's specific causation opinion was nothing more than unsupported *ipse dixit*. Indeed, Dr. Delacroix admitted that "day in and day out" he sees bladder cancer patients who look like Mr. Allen (white male, 50 years old or older, non-smoker) but who did not take Actos. (Ex. 33, Vol. XIX, 02/28/14 Tr. at 2813:22 – 2814:1). He also testified that the absolute risk of bladder cancer from Actos is "relatively low" (*id.* at 2801:9-21), and that Mr. Allen's bladder tumor would look no different than a bladder tumor in a non-Actos patient (*id.* at 2806:23 – 2807:10). Given those concessions, Dr. Delacroix's opinion does not constitute the "substantial evidence" of specific causation necessary to sustain the jury's verdict on any of Plaintiffs' claims.[17] Therefore, the Court should enter judgment in favor of Defendants on all of Plaintiffs' claims.

Moreover, as the Supreme Court has held, "[i]nadmissible evidence contributes nothing to a 'legally sufficient evidentiary basis.'" *Weisgram* v. *Marley Co.*, 528 U.S. 440, 454 (2000). When expert testimony is "not supported by sufficient facts to validate it in the eyes of the law, or . . . indisputable record facts contradict or otherwise render the opinion unreasonable, it cannot support a jury's verdict." *Brooke Grp. Ltd.* v. *Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993). Because Dr. Delacroix's testimony does not survive *Daubert*, (*see* Memorandum and Reply In Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Dr. Scott Delacroix), it cannot serve as the sole basis for finding specific causation and

[17] Dr. Delacroix also offered the incredible opinion that Actos can cause bladder cancer within two to three weeks of use. (Ex. 33, Vol. XIX, 02/28/14 Tr. at 2738:9 – 2739:15).

imposing billions of dollars in liability on two companies that marketed a life-saving drug that Plaintiff's own physicians continue to prescribe. Therefore, the jury's verdict cannot stand.

4. Plaintiffs' breach of implied warranty claim against Takeda also fails as a matter of law because Plaintiffs did not present evidence that Actos is unfit for its intended purpose or is not minimally safe.

Plaintiffs' breach of implied warranty claim fares no better. Under New York law, the sale of most goods includes an implied warranty of merchantability. *See* McKinney's Uniform Commercial Code § 2-314. This implied warranty "does not mean that the product will fulfill [a] buyer's every expectation." *Denny v. Ford Motor Co.*, 662 N.E.2d 730, 736 n.4 (N.Y. 1995) (alteration in original). Instead, it means only that the product is "fit for the ordinary purposes for which such goods are used" and "minimally safe for its expected purpose." *Id.* at 736.

The ordinary purpose for which Actos is used is to improve glycemic control in patients with type 2 diabetes. Plaintiffs did not offer any evidence that Actos is unfit for that purpose. To the contrary, Actos maintains its FDA approval for that purpose to this day, and Plaintiffs told the jury that they are not claiming that Actos should be taken off the market. (Ex. 22, Vol. II, 02/03/14 Tr. at 24:17-18 (opening statement) ("You'll see this is not a case where we're saying, take Actos off the market.")). And, all three of the physicians who have treated Mr. Allen for diabetes testified that they still prescribe Actos to some of their patients today.[18] Moreover, the undisputed evidence shows that all diabetes medications have risks (some potentially fatal), (Ex. 45, Dr. Reilly Testimony, P7512A at 50:13-20; Ex. 46, Dr. Lamb Testimony, P7514A at 44:5 – 45:19), and that the absolute risk of developing bladder cancer while taking Actos is low (*see* Ex. 33, Vol. XIX, 02/28/14 Tr. at 2801:9-15 (Plaintiffs' expert, Dr. Delacroix, agreeing that "the risks [of bladder cancer] associated with pioglitazone are, in absolute terms, low"); Ex. 35, Vol.

[18] (Ex. 45, Dr. Reilly Testimony, P7512A at 50:7-12; Ex. 46, Dr. Lamb Testimony, P7514A at 51:7-52:24; Ex. 47, Dr. Wnek Testimony, D2781A at 30:5-8).

XXII, 03/12/14 Tr. at 3164:7-19, 3171:1-19 (Plaintiffs' expert, Dr. Schneeweiss, agreeing that a study that he described as "high quality" found that Actos presented a "low absolute risk[]" of bladder cancer)).

This record is inconsistent with a finding that Actos – a socially beneficial drug that Plaintiffs concede should stay on the market – is unfit for its ordinary purposes and not minimally safe. *See In re Fosamax Prods. Liab. Litig.*, 924 F. Supp. 2d 477, 488-89 (S.D.N.Y. 2013) (New York law) (ruling that although there was a dispute of fact on whether the manufacturer of an osteoporosis drug had adequately warned about the drug's potential risk of osteonecrosis of the jaw (dead bone in the jaw, "ONJ"), the manufacturer was entitled to judgment on plaintiff's breach of implied warranty claim because the evidence showed that the drug was effective for the treatment of osteoporosis and "the risk for ONJ is small"); *Daley v. McNeil Consumer Prods. Co.*, 164 F. Supp. 2d 367, 374-75 (S.D.N.Y. 2001) (New York law) (breach of implied warranty claim failed where no "more than a microscopic fraction of potential users" reported an adverse reaction). Therefore, Takeda is entitled to judgment on Plaintiffs' breach of implied warranty claim.

5. Plaintiffs' demand for punitive damages fails as a matter of law because Plaintiffs did not show that Defendants engaged in a wanton disregard of safety.

Even less defensible than the finding of liability are the astronomical punitive damages awards. The New York "standard for imposing punitive damages is a strict one," *Marinaccio v. Town of Clarence*, 986 N.E.2d 903, 906 (N.Y. 2013), and New York permits punitive damages awards only in "singularly rare cases." *Garrity v. Lyle Stuart, Inc.*, 353 N.E.2d 793, 797 (N.Y. 1976). *See also, e.g., In re Eighth Judicial Dist. Asbestos Litig.*, 938 N.Y.S.2d 715, 716 (App. Div. 2012) ("We conclude that this is not one of those singularly rare cases where punitive damages are warranted."). To win a punitive damages award, a New York plaintiff "must" show

that defendant engaged in misconduct that was "exceptional" and demonstrated a "reckless or wanton disregard of [the] safety or rights" of others. *Ross v. Louise Wise Services, Inc.*, 868 N.E.2d 189, 196 (N.Y. 2007). The alleged misconduct supporting punitive damages must "imply a criminal indifference to civil obligations." *Marinaccio*, 986 N.E.2d at 906; *Ross*, 868 N.E.2d at 196.[19]

Plaintiffs did not allege that the mere selling of Actos constituted a wanton disregard for the safety of others. To the contrary, in opening statements they told the jury "this is not a case where we're saying, take Actos off the market." (Ex. 22, Vol. II, 02/03/14 Tr. at 24:17-18). Indeed, the undisputed evidence showed that Actos is commonly prescribed and effective in treating diabetes,[20] "a horrific" and "nasty, nasty, deadly disease," (Ex. 22, Vol. II, 02/03/14 Tr. at 36:2, 42:17) (Plaintiffs' opening statement), and while Plaintiffs' experts testified that Actos presents a potential risk of bladder cancer, they said that risk is "low." (Ex. 33, Vol. XIX, 02/28/14 Tr. 2801:9-15 (Dr. Delacroix agreeing that "the risks [of bladder cancer] associated with pioglitazone are, in absolute terms, low"); Ex. 34, Vol. XXII, 03/12/14 Tr. at 3164:7-19, 3171:1-19 (Dr. Schneeweiss agreeing that a study that he described as "high quality" found that Actos presented a "low absolute risk[]" of bladder cancer)).

Rather than contend that the mere selling of Actos constituted a wanton disregard for the safety of others, Plaintiffs contended that Defendants wantonly disregarded the safety of others by not adequately warning prescribing physicians that Actos presents a low potential risk of bladder cancer. But, it is undisputed that the Actos label (which is written for physicians) has

[19] As Defendants have argued, (*see, e.g.*, Ex. 39, Vol. XXXVI, 04/04/14 Tr. 5979:11-22), New York law requires plaintiffs to establish wanton disregard of safety by clear and convincing evidence. But, regardless of the standard of review, plaintiffs have failed to meet their burden.

[20] All three of the physicians who have treated Mr. Allen for diabetes testified that they still prescribe Actos to some of their patients today. (Ex. 45, Dr. Reilly Testimony, P7512A at 50:7-12; Ex. 46, Dr. Lamb Testimony, P7514A at 51:7-52:24; Ex. 47, Dr. Wnek Testimony, D2781A at 30:5-8).

always contained information about bladder cancer. The Precautions section of the very first Actos label, approved by the FDA in 1999, stated that bladder tumors "were observed in male rats" given doses "approximately equal to the maximum recommended human oral dose." (Ex. 6, 07/99 Actos Label, D1067 at 12). In 2006 – approximately four and a half years before Mr. Allen was diagnosed with bladder cancer – Takeda added human bladder cancer data to the Precautions section of the Actos label, noting that in the two 3-year clinical trials of Actos (the longest clinical trials of Actos) "there were 16/3656 (0.44%) reports of bladder cancer in patients taking" Actos "compared to 5/3679 (0.14%) in patients not taking" Actos, and that "[a]fter excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on" Actos "and two (0.05%) on placebo." (Ex. 14, 08/06 Actos Label, D1626 at 16). In 2009 – more than a year before Mr. Allen was diagnosed with bladder cancer – The Actos Medication Guide (which is written for patients) was revised to state: "In studies of pioglitazone (the medicine in ACTOS), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone." (Ex. 15, 09/09/09 letter from FDA to Takeda, D1916 at 1 and 7 (approving addition of bladder cancer language to Medication Guide)).

The inclusion of this safety information about bladder cancer in the Actos labeling was the *opposite* of a "reckless or wanton disregard" for the safety of others. Courts in New York and elsewhere have rejected the notion that a manufacturer can be held liable for punitive damages under a "reckless or wanton disregard" standard where the product label (including the Precautions section of a drug label) included information about the very safety concern at issue. *See In re Fosamax Prods. Liab. Litig.*, 924 F. Supp. 2d at 490 (New York law) (granting

prescription drug manufacturer's motion for summary judgment on punitive damages; manufacturer did not engage in "wanton disregard" of "the safety of others" where it "inform[ed] the medical community" of the risk at issue through the Precautions section of the drug's label); *see id.* at 494, 497 (noting that the risk at issue was discussed in the Precautions section of the Fosamax label); *DeLuryea v. Winthrop Labs.*, 697 F.2d 222, 230-31 (8th Cir. 1983) (stating "there was no evidence to support punitive damages" under a "malice, wantonness, or reckless indifference" standard where the Precautions section and the Adverse Reactions section of a prescription drug label mentioned the risk at issue (tissue damage) at the time plaintiff took the drug);[21] *Krister v. Beech Aircraft Corp.*, 470 F.2d 1089, 1096-97 (5th Cir. 1973) (even though manufacturer's warning was not adequate to absolve it from compensatory liability, "[t]he fact that the" manufacturer took "steps to inform" plaintiff "of potential danger absolved" manufacturer of liability "for punitive" damages).[22]

[21] In *DeLuryea*, the plaintiff took the drug at issue from August 1968 to June 1974. *Id.* at 224, 227. From September 1968 to May 1974, the drug label's Adverse Reactions section mentioned tissue damage. *Id.* at 230 n.7. In May 1974 – the month before plaintiff stopped taking the drug – the manufacturer added tissue damage to the Precautions section of the label. *Id.*

[22] *See also In re Levaquin Prods. Liab. Litig.*, 700 F.3d 1161, 1169 (8th Cir. 2012) (even though there was a dispute of fact on whether the drug manufacturer's warning label was adequate, manufacturer was entitled to judgment on demand for punitive damages because the warning showed that the manufacturer did not "deliberately disregard[] the risk"); *Heston v. Taser Int'l, Inc.*, 431 F. App'x 586, 589 (9th Cir. 2011) ("Here, [defendant] made efforts, albeit insufficiently, to warn its customers about the risks posed by [the product.] While this may amount to negligence, it does not rise to the level of willful or wanton conduct."); *Dudley v. Bungee Int'l Mfg. Corp.*, 1996 WL 36977, at *3 (4th Cir. Jan. 31, 1996) (although manufacturer could be held liable on plaintiff's negligence claims, manufacturer was entitled to judgment as a matter of law on plaintiff's demand for punitive damages; manufacturer did not engage in "wanton" disregard for others where product's packaging, "at least in general terms, warned others of the" potential "dangers" at issue); *Richards v. Michelin Tire Corp.*, 21 F.3d 1048, 1059 (11th Cir. 1994) ("We have repeatedly held that the issue of punitive damages should not go to the jury when a manufacturer takes steps to warn the plaintiff of the potential danger that injured him; such acts bar a finding of wantonness."); *Toole v. McClintock*, 999 F.2d 1430, 1433, 1435-36 (11th Cir. 1993) (even though "jury could have reasonably thought that [medical device manufacturer's] warning, as it was worded, understated the risks," manufacturer's conduct could not "be viewed as wanton" because the "warning describe[d] the main harms that [plaintiff] actually suffered"); *West v. Goodyear Tire & Rubber Co.*, 973 F. Supp. 385, 388-89 (S.D.N.Y. 1997) (New York law) (granting tire manufacturer's motion for summary judgment on punitive damages; manufacturer's conduct was not "wanton or reckless" even though "the

Plaintiffs offered various criticisms of Defendants' actions. But, even if those criticisms supported liability on Plaintiffs' compensatory claims (which they do not), none of those criticisms demonstrate that Defendants wantonly disregarded patient safety.

For example, Plaintiffs contended that the human bladder cancer data should have gone into the Warnings section of the label, rather than the Precautions section. But, Dr. Reilly (one of the physicians who prescribed Actos to Mr. Allen) agreed that "information in the Precautions section would be important for a physician trying to make a decision on whether to prescribe a drug." (Ex. 45, Dr. Reilly Testimony, P7512A at 60:5-11). Indeed, Dr. Reilly testified that he had read the Precautions section of the August 2006 label. (*Id.* at 59:11-19). And, Dr. Lamb (another one of the physicians that prescribed Actos to Mr. Allen) agreed that the 2006 Precaution about bladder cancer "provides a type of information that [she] would need as a physician to prescribe [Actos]." (Ex. 46, Dr. Lamb Testimony, P7514A at 65:20 – 67:20).

Moreover, the evidence showed that *the FDA* recommended the label's language regarding the human bladder cancer data, and that *the FDA* told Takeda to put that language in the Precautions section. (*See, e.g.*, Ex. 12, 07/28/06 FDA Approval Package for Duetact (a product containing Actos), D1621 at 4, 25-26, 45-46, 53-64, 170-74; Ex. 37, Vol. XXXII, 03/28/14 Tr. 5160:14 – 5162:25 (Feigal)). The FDA took those actions after Takeda provided the FDA with a wealth of data regarding Actos and bladder cancer, including, among other things, data from Actos clinical trials (including the PROactive trial) and the first interim report from the KPNC study – an ongoing, 10-year epidemiological study of bladder cancer in Actos

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lettering on the warning" was "small" and the manufacturer "did not choose to use all possible methods of warning").

patients.[23] A drug manufacturer does not wantonly disregard patient safety by following the FDA's direction on a label change, especially when that direction comes after the FDA has thoroughly reviewed the data collected by the manufacturer.[24]

Plaintiffs also blasted Takeda for undertaking the KPNC study, and said that instead of doing a long-term epidemiological study like KPNC, Takeda should have undertaken and provided the FDA with a meta-analysis of the bladder cancer cases in all of the Actos clinical trials because such a meta-analysis would have prompted the FDA to order Takeda to put human

[23] (*See, e.g.*, Ex. 9, 08/31/05 Takeda submission of bladder cancer data to FDA, D1501; Ex. 10, 06/01/06 Takeda submission of bladder cancer data to FDA, D1584). Takeda notes that its August 2005 submission to FDA included analyses of the PROactive bladder cancer data and the first interim KPNC data from four outside specialists – Dr. David Phillips, Professor of Environmental Carcinogenesis at the Institute of Cancer Research in the United Kingdom; Dr. Samuel Cohen, Professor and Chair of Pathology and Microbiology at the University of Nebraska Medical Center; Dr. Paul Stang of Galt Associates, Inc. and Adjunct Researcher and Lecturer in Epidemiology at the University of North Carolina and the University of Pennsylvania; and Dr. Michael Droller, Professor of Urology at the Mount Sinai Medical Center in New York City. (*See* Ex. 9, 08/31/05 Takeda submission of bladder cancer data to FDA, D1501 at 9, 20 – 33). The fact that Takeda hired these highly qualified outside specialists to analyze the data is inconsistent with a finding that Takeda wantonly disregarded patient safety.

[24] Plaintiffs contend that FDA regulations required the human bladder cancer data to go in the Warnings section of the label, rather than the Precautions section. But, "[c]ourts are required to give substantial deference to an agency's interpretation of its own regulations," *Girling Health Care, Inc. v. Shalala*, 85 F.3d 211, 215 (5th Cir. 1996), and the FDA's 2006 labeling action demonstrates that the FDA does not agree with Plaintiffs' interpretation of the FDA regulation. Moreover, Plaintiffs are also wrong in their belief that a Precaution cannot satisfy as manufacturer's duty to warn. *Martin v. Hacker*, 628 N.E.2d 1308 (N.Y. 1993), makes clear that the manufacturer's "warning" includes the entire label, not just the Warnings section of the label. Throughout that opinion, the *Martin* court capitalized "Warning" when talking about the Warnings section of the label, but did not capitalize "warning" when talking about whether the label adequately warned of the drug's potential risks. The *Martin* court also cited information in the Actions, Adverse Reactions and Dosage & Administration sections of the label when ruling that the labels in question adequately "warned" prescribing physicians about the drug's potential risks. *See id.* at 1314-15. *See also, e.g.*, *Saraney v. TAP Pharm. Prod., Inc.*, 2007 WL 148845, at *6 (N.D. Ohio Jan. 16, 2007) (drug label was adequate as a matter of law where it warned of risk at issue in the "Precautions" and "Adverse Reactions" sections); *Taylor v. Pharmacia-Upjohn Co.*, 2005 WL 3502052, at *5 (S.D. Miss. Dec. 19, 2005) (finding that "warnings as to … potential side effects" included information contained in the "Precautions" and "Adverse Reactions" sections of a prescription drug label); *Percival v. American Cyanamid Co.*, 689 F. Supp. 1060, 1063-64 (W.D. Okla. 1987) (vaccine's label was adequate as a matter of law because the injury at issue was listed in the label's Adverse Reactions section). In any event, as the Fifth Circuit has noted, "a claim that [a drug manufacturer] breached a federal labeling obligation sounds exclusively in federal (not state) law, and is preempted." *Morris*, 713 F.3d at 777.

bladder cancer data in the Warnings section of the label. Plaintiffs' arguments about KPNC and a meta-analysis are without merit.

Plaintiffs' argument about KPNC fails because the undisputed evidence showed that: (1) the FDA agreed with Takeda that a long-term epidemiological study was an appropriate way to examine the issue of bladder cancer in Actos patients;[25] (2) Takeda hired, in the words of one of Plaintiffs' own expert witnesses, "highly talented scientists," to design and run KPNC;[26] and (3) the FDA provided input on, and approved the design of, KPNC.[27] Those facts are flatly inconsistent with a finding of wanton disregard of safety. *See Marinaccio*, 986 N.E.2d at 906 (New York Court of Appeals ruling that although defendant real estate developer acted negligently in its design of a storm water remediation plan that resulted in flooding of another landowner's property, defendant's "actions could not be considered wanton and reckless" where defendant, in designing the plan, "worked closely with the U.S. Army Corps of Engineers" and "hired a wetlands expert, an engineering expert, and soil expert").[28]

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[25] (Ex. 7, 02/04/03 Meeting Minutes, D1218 (summarizing meeting between Takeda and FDA that included discussion of, among other things, conducting the KPNC study); Ex. 8, 03/24/04 Takeda letter to FDA, D1330 (responding to FDA's comments on original proposed KPNC protocol)).

[26] Plaintiffs' expert epidemiologist, Dr. Schneeweiss, testified that the KPNC investigators "are highly talented scientists." (Ex. 35, Vol. XXII, 03/12/14 Tr. at 3143:14-17). Indeed, the lead KPNC investigator – Dr. Brian Strom of the University of Pennsylvania's Center for Clinical Epidemiology and Biostatistics – is the editor of a textbook entitled *Pharmacoepidemiology* and has served as the president of the International Society of Pharmacoepidemiology ("ISP"). Plaintiffs did not dispute that those credentials are impressive because Dr. Schneeweiss contributed a chapter to Dr. Strom's book and has also served as the president of ISP. (*See* Ex. 34, Vol. XXI, 03/11/14 Tr. at 2916:25 – 2917:7, 3034:8-11 (Schneeweiss); Ex. 35, Vol. XXII, 03/12/14 Tr. 3092:3-14 (Schneeweiss)).

[27] (*See* Ex. 8, 03/24/04 Takeda letter to FDA, D1330 (responding to FDA's comments on proposed KPNC protocol); Ex. 9, 08/31/05 Takeda submission of bladder cancer data to FDA, D1501 at 2 (referring to Takeda's "agreement with the Agency to conduct an epidemiological study to assess the risk of bladder cancer in type 2 diabetes patients exposed to pioglitazone")).

[28] It is also undisputed that Takeda performed an extension of the PROactive clinical trial to examine over the course of ten years whether Actos increased the risk for bladder cancer. One of Plaintiffs' experts, Dr. Delacroix, said the PROactive extension was "[h]igh quality epidemiology" with a "laudable goal." (Ex. 31, Vol. XVII, 02/26/14 Tr. at 2438:11-14, 2439:6-7). While Plaintiffs' experts offered criticisms of some (but not all) aspects of the designs of KPNC and the PROactive extension, the fact that the studies

Plaintiffs' argument about a meta-analysis also fails because the undisputed evidence showed that a meta-analysis of all the Actos clinical trials would not have prompted the FDA to order that bladder cancer data go into the Warnings section of the Actos label.

First, in 2006, the FDA did a combined analysis of the two 3-year Actos clinical trials (the longest Actos clinical trials) and, even though that analysis showed a statistically significant difference between the number of bladder cancer cases in Actos patients and the number of bladder cancer cases in non-Actos patients, the FDA did not direct Takeda to put human bladder cancer data in the Warnings section of the label at that time. Instead, it directed Takeda to put that data in the Precautions section of the label. [29]

Second, although Takeda conducted a meta-analysis of all the Actos clinical trial data at the request of European regulators in 2011 and provided that meta-analysis to the FDA in May 2011,[30] that meta-analysis did *not* prompt the FDA to order that bladder cancer data go in the Warnings section of the label. Instead, it was the third interim KPNC data that prompted the FDA to order that bladder cancer data (specifically, the third interim KPNC data) go into the "Warnings and Precautions" section in 2011 – after the Actos label had been converted to the

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were conducted is inconsistent with a finding of a wanton disregard of the rights and safety of others. *Marinaccio*, 986 N.E.2d at 906. *See also Roginsky v. Richardson-Merrell, Inc.*, 378 F.2d 832, 843 (2d Cir. 1967) (New York law) (stating that although a drug manufacturer might be liable for punitive damages if "the manufacturer was shown to have become aware of danger and *to have done nothing, deliberately closing its eyes*," the manufacturer should not be liable for punitive damages simply because its affirmative actions in response could have been different) (emphasis added).

[29] (*See* Ex. 12, 07/28/06 FDA Approval Package for Duetact (a product containing Actos), D1621 at 53-64 (conducting combined analysis of bladder cancer data from the two 3-year Actos clinical trials and stating that the data should be added to the Precautions section after that section's discussion of rat bladder cancer data); Ex. 37, Vol. XXXII, 03/28/14 Tr. 5160:14 – 5162:25 (Feigal); Ex. 13, 08/30/06 letter from FDA to Takeda, D1639 at 1 and 18 (approving the addition of Actos human clinical trial data regarding bladder cancer to the Precautions section of the Actos label)).

[30] (*See* Ex. 29, Vol. XI, 02/14/14 Tr. at 1450:24 – 1451:1, 1527:24 – 1528:2 (Kessler); Ex. 30, Vol. XVI, 02/24/14 Tr. at 2328:9-10 (Madigan)).

new "PLR" format.[31] To this day, the FDA has never directed Takeda to put the 2011 meta-analysis in the Actos label.

It is unsurprising that the FDA has not directed that the meta-analysis be put in the label. In the two 3-year clinical trials of Actos, there were 16 cases of bladder cancer in Actos patients and 5 cases of bladder cancer in patients not taking Actos. The FDA has long taken the position that these were "too few events of bladder cancer to establish causality." (*See, e.g.*, Ex. 19, 07/11 Actos Label, P2456 at 18)). The 2011 meta-analysis added all of the other Actos clinical trials to the mix, but among all those other clinical trials, there were only 3 additional cases of bladder cancer in Actos patients and 2 additional cases of bladder cancer in patients not taking Actos.[32] This additional data actually showed a smaller difference between Actos patients and non-Actos patients than did the FDA's 2006 combined analysis of the data from the two 3-year clinical trials.[33]

In short, the meta-analysis issue was a red herring. The FDA relied on the KPNC data, not the meta-analysis data, when directing a label change. The fact that Takeda provided the meta-analysis to the FDA and that it made no difference to the FDA undermines Plaintiffs' argument that Takeda acted with wanton disregard for patient safety by not performing the meta-analysis before 2011.

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[31] (*See* Ex. 16, 01/25/10 letter from Takeda to the FDA, D1943 at 1-2 (submitting the third interim (5-year) analysis of KPNC to the FDA); Ex. 17, 09/17/10 FDA Drug Safety Communication: Ongoing Safety Review of Actos (pioglitazone) and Potential Increased Risk of Bladder Cancer After Two Years Exposure, D1977 at 1 (stating that FDA "is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether Actos (pioglitazone), is associated with an increased risk of bladder cancer"); *id.* at 3 (stating that the FDA would "complete" its review "in several months"); Ex. 19, 07/11 Actos Label, P2456 at 6 (discussing the 5-year interim analysis of KPNC)).

[32] (Ex. 18, 05/13/11 Takeda Meta-Analysis, D2053 at 25, Table 11.d).

[33] (*Compare* Ex. 12, 07/28/06 FDA Approval Package for Duetact (a product containing Actos), D1621 at 59 (calculating odds ratio of 3.24) *with* Ex. 18, 05/13/11 Takeda Meta-Analysis, D2053 at 25 (calculating hazard ratio of 2.642)).

Speaking of red herrings, Plaintiffs spent countless hours of trial time devoted to other topics having nothing to do with the underlying issue on punitive damages – *i.e.*, whether defendants engaged in wanton misconduct that proximately caused Mr. Allen to develop bladder cancer. It is well settled that in order for a defendant's actions to be a basis for an award of punitive damages, those actions must have been a proximate cause of plaintiff's injuries. *See Taylor v. Dyer*, 593 N.Y.S.2d 122 (App. Div. 1993) (stating that although defendant's conduct "might be considered reprehensible," it could not support a punitive damages award because it "did not proximately cause plaintiffs' injuries").[34] Defendants contend that they acted appropriately at all times, and there is no dispute that Defendants marketed a socially beneficial drug that should remain on the market and that Mr. Allen's own physicians continue to prescribe to some of their patients. But, even if Plaintiffs' various accusations of misconduct were true, none of that alleged misconduct was a proximate cause of Mr. Allen's bladder cancer.

For example, Plaintiffs accused Lilly and Takeda of sponsoring the "ghostwriting" of scientific articles about Actos. Even if those accusations were true, Plaintiffs offered no evidence that Mr. Allen's prescribing physicians read the allegedly ghostwritten articles, let alone that those articles played a part in the prescribing physicians' decisions to prescribe Actos to Mr. Allen.

[34] *See also, e.g., Lamb v. Mendoza*, 478 F. App'x 854, 857 (5th Cir. 2012) (stating that plaintiff was not entitled to a jury instruction on punitive damages because defendants' alleged "reckless disregard" for plaintiff's health was not a "proximate cause" of plaintiff's injury); *Ventas, Inc. v. HCP, Inc.*, 647 F.3d 291, 319 (6th Cir. 2011) (stating the "law requires a plaintiff seeking punitive damages to prove that the relevant actions of the defendant were the proximate cause of the resulting injury to the plaintiff"); *Stogsdel v. Healthmark Partners, L.L.C.*, 377 F.3d 827, 832 (8th Cir. 2004) (finding error where the jury may have "base[d] its punitive damages award on evidence unrelated to the treatment [plaintiff] received"); *Bauerlein v. Equity Residential Properties Mgmt. Corp*, 2007 WL 1793578, at *6 (D. Ariz. June 19, 2007) ("It is well established that conduct giving rise to punitive damages must be a proximate cause of the harm inflicted.").

Other examples include Plaintiffs' attack on Dr. Cohen's explanation for the development of bladder tumors in rats during the preclinical testing of Actos, and Plaintiffs' allegation that Actos is a dual PPAR agonist rather than a PPAR gamma agonist. Although Plaintiffs argued that Dr. Cohen's explanation for the rat data was wrong, Plaintiffs never argued that their own interpretation of the rat data should have elevated bladder cancer to the Warnings section of the label. Instead, they argued that it was the later human data which should have elevated bladder cancer to the Warnings section. In other words, Takeda's belief in Dr. Cohen's explanation was not a proximate cause of Mr. Allen's injury. Plaintiffs also argued that Actos is a dual PPAR agonist, not a PPAR gamma agonist. But, Plaintiffs presented no evidence that Actos' PPAR affinity played any role in Dr. Reilly's or Dr. Lamb's decision to prescribe Actos to Mr. Allen. Indeed, both physicians continue to prescribe Actos. Therefore, even if Defendants had a duty to market Actos as a dual PPAR agonist rather than a PPAR gamma agonist (which they did not), the marketing of Actos as a PPAR gamma agonist was not a proximate cause of Mr. Allen's injury.[35]

Plaintiffs also presented evidence that Takeda chose to proceed with the development of Actos after Upjohn decided to discontinue its work on Actos in 1993, and that Takeda provided Upjohn with proposed written language for Upjohn to use when it notified the FDA of its decision to stop work on Actos. However, none of Takeda's actions with respect to Upjohn supports a punitive damages award. As an initial matter, Plaintiffs presented no evidence that it was inappropriate for Takeda to continue the development of Actos after Upjohn stopped

[35] Another red herring was Takeda's signal of disproportionate reporting ("SDR") analysis comparing bladder cancer reports in Actos patients with bladder cancer reports in patients taking any of the other 11,000 drugs approved in the United States. Plaintiffs presented no evidence that the FDA would have elevated bladder cancer to the Warning section had Takeda submitted that SDR analysis. (*See* Ex. 27, Vol. IX, 02/12/14 Tr. 1179:6 – 1187:10). In any event, Plaintiffs cannot base any claim, let alone one for punitive damages, for alleged withholding of information from the FDA. *See Buckman*, 531 U.S. 341; *Lofton*, 672 F.3d at 380.

working on the project, let alone that Takeda's decision to continue the development of Actos was a wanton or reckless one. Indeed, any allegation that Takeda acted inappropriately by continuing to develop Actos would be at odds with Plaintiffs' statement that they were not asserting that Actos should be taken off the market. Moreover, the undisputed evidence is that Upjohn's Program Manager for Actos – Patricia Ruppel – said that Takeda's proposed statement "reflect[ed] pretty accurately" the basis for Upjohn's decision to stop working on Actos.[36] In any event, it is undisputed that Upjohn's decision to stop working on Actos had nothing to do with bladder cancer. (*See* Ex. 36, Vol. XXVIX [sic], 03/25/14 Tr. at 4668:4-7 (Plaintiffs' counsel stating: "I've never made the inference or the implication there was anything to do with bladder cancer in the Upjohn study, so we'll set that aside, now, okay?")).[37] This is a *bladder cancer* case. Therefore, Plaintiffs cannot seek any damages, let alone punitive damages, for an alleged failure to warn about risks of injuries other than bladder cancer.[38]

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[36] (Ex. 2, 10/27/93 email from P. Ruppel to P. Daniels, P106 ("Actually, this [proposed statement from Takeda] reflects pretty accurately the stand that [Upjohn] presented to Takeda in Osaka. There are preclinical issues and the amount of preclinical work that would be needed to address these issues and the modest clinical efficacy that has been seen do not justify development in accordance with Upjohn's business needs.").

[37] Plaintiffs' counsel later introduced a 1986 Upjohn report on a 90-day study of Actos in beagles which noted a "small slightly depressed red spot on the mucosa" of one dog's bladder. (Ex. 1, 10/14/86 Upjohn Technical Report, P7442 at 35). During closing, Plaintiffs' counsel argued that this report showed that Upjohn "knew there were serious safety issues that might include bladder [cancer], might include a lot of things that needed to be studied." (Ex. 40, Vol. XXXVII, 04/07/14 Tr. at 6140:21 – 6141:4). That argument was another red herring. Plaintiffs presented no evidence that Upjohn or Takeda did or should have interpreted a small dot on a single dog's bladder as indicating a potential risk of bladder cancer. More importantly, the undisputed evidence is that Takeda subsequently performed animal carcinogenicity studies of Actos, including studies looking at the issue of bladder cancer, and that the FDA reviewed those studies before it approved Actos. (*See e.g.*, Ex. 4, 06/30/99 FDA Pharmacology Reviews of Takeda's New Drug Application for Actos, D1065 at 2-5, 39-49, 52-117 (evaluations of animal carcinogenicity studies); Ex. 5, 06/30/99 Telefax from FDA to Takeda, D1064 (FDA's proposed changes to the Actos label's discussion of animal carcinogenicity studies); Ex. 37, Vol. XXXII, 03/28/14 Tr. at 5144:10 – 5146:11 (Dr. Feigal discussing D1064)). Put simply, the 1986 Upjohn report offers no support for a punitive damages verdict.

[38] Under New York law, a "manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew, or, in the exercise of reasonable care, should have known to exist." *Martin v. Hacker*, 628 N.E.2d at 1311. However, New York law is also clear that a plaintiff cannot recover damages for a

Plaintiffs also devoted five days of the trial to the issue of spoliation. But, Takeda's alleged spoliation of evidence does not support a punitive damages verdict.

As an initial matter, New York does not recognize a cause of action for spoliation of evidence, *see, e.g.*, *Mohammed v. Delta Airlines, Inc.*, 2011 WL 5554269, at *2 (E.D.N.Y. Nov. 15, 2011) ("New York does not recognize an independent cause of action for spoliation"),[39] and New York courts have expressed skepticism on whether spoliation of evidence may form the basis for a punitive damages award under New York law, *see Reuven Enter. Sec. Div., LLC v. Synergy Inv. Group, LLC*, 2013 N.Y. Misc. LEXIS 2049, at *8 (N.Y. Supr. Ct. Mar. 27, 2013) ("spoliation of evidence may be sanctionable but it typically does not form a basis for punitive damages, absent some proof of willful or wanton conduct"); *Blumenthal v. Zacklift Intern., Inc.*, 2008 N.Y. Misc. LEXIS 9618, at *41 (N.Y. Supr. Ct. Jun. 4, 2008) ("plaintiffs point to no case law authority that would allow the court to award punitive damages as a sanction for spoliation of evidence"). In addition, as Takeda has argued repeatedly, it had no duty to preserve documents for bladder cancer litigation until July 2011 – after Mr. Allen suffered his injury. (*See, e.g.*, Takeda's Opposition to Plaintiffs' Spoliation and Rule 37 Motion for Sanctions).

In any event, Plaintiffs presented no evidence from which a reasonable jury could conclude that the failure to preserve custodial files (emails, PowerPoint presentations, *etc.*) of various Takeda employees when those employees left Takeda was done with the intent to hide

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defendant's breach of a duty unless *that breach* was the proximate cause of plaintiff's injury. *See Becker v. Swartz*, 386 N.E.2d 807, 811 (N.Y. 1978) ("As in any cause of action founded upon negligence, a successful plaintiff must demonstrate the existence of a duty, *the breach of which* may be considered the *proximate cause* of the damages suffered by the injured party.") (emphases added). *See also, e.g., Smith v. Stark*, 490 N.E.2d 841, 842 (N.Y. 1986) (defendant was entitled to judgment as a matter of law because its alleged failure to warn "was not the proximate cause of plaintiff's injuries"). Thus, even if Defendants breached a duty to warn about a potential risk other than bladder cancer, Plaintiffs cannot recover damages (compensatory or punitive) for that breach because that breach was not a proximate cause of Plaintiffs' injuries.

[39] *See also Hillman v. Sinha*, 910 N.Y.S.2d 116 (App. Div. 2010) (agreeing that "New York does not recognize an independent cause of action to recover damages for negligent spoliation of evidence").

evidence that Actos increases the risk of bladder cancer. Indeed, Plaintiffs said in their opening statement that they were not accusing Takeda of deliberating shredding documents as part of a cover up. (Ex. 22, Vol. II, 02/03/14 Tr. at 52:21-25). And, for the following reasons, any conclusion by the jury that Takeda destroyed custodial files of former employees with the intent to hide evidence that Actos increases the risk for bladder cancer is wholly unsupported.

First, evidence that use of a drug increases the risk for a disease comes in the form of *scientific data*, such as randomized clinical trial data and epidemiological data. *See generally*, Federal Judicial Center, *Reference Manual on Scientific Evidence* 549-632 (3d ed. 2011). (*See also* Ex. 26, Vol. VIII, 02/11/14 Tr. at 1005:19-25 and Ex. 27, Vol. IX, 02/12/14 Tr. at 1085:4-6 (Dr. Kessler describing randomized clinical trials as the "gold standard" for determining causation)). In other words, scientific data – not employee emails and PowerPoint presentations – prove causation. And, it is undisputed that: (1) Takeda stores its scientific data regarding Actos in databases; (2) Takeda produced the data from those databases to Plaintiffs;[40] and (3) Plaintiffs have made no allegation, let alone presented evidence, that data was missing from those databases.

Second, even if evidence of causation came from employee custodial files, any scheme to cover up that evidence over a period of several years through employee attrition (*i.e.*, by deleting custodial files when employees leave the company) would be spectacularly ill-conceived because there would be no way to know whether all key employees with documents relevant to the issue of bladder cancer would leave the company before bladder cancer litigation ensued. Indeed, it is undisputed that a number of key Takeda employees with documents relevant to bladder cancer

[40] (*See* Ex. 20, Exhibit A to 06/03/13 Declaration of Stacey Dixon Calahan, D2690 at 8-9 (list of Takeda databases produced to Plaintiffs); Ex. 25, Vol. VII, 02/10/14 Tr. at 847:25 – 848:17 (Ms. Calahan discussing production of Takeda databases)).

did not leave Takeda before the bladder cancer litigation hold was put in place in 2011 and that Takeda preserved (and produced) those employees' custodial files.[41]

Third, it is common knowledge that deleting an email from a person's email files would not necessarily destroy that email permanently (or any documents attached to that email) because the email is also likely to be in the email files of at least one other person (in the "in-box" or the "sent-box"). In other words, it would be a fool's errand to try to hide a "smoking gun" email by simply deleting an employee's email file when that employee leaves the company. In fact, it is undisputed that several thousand emails and attachments of the former employees at issue (the "no file custodian" ("NFCs")) were in fact preserved because those documents were also located in the email files of at least one other Takeda employee (and Takeda produced those documents to Plaintiffs). (*See* Ex. 21, No File Custodian Summary Sheets List Updated Sept. 14, 2013, P5303). For example, although Mr. Miyazaki's custodial files were not preserved when he left the company, over 81,000 emails and email attachments (totaling nearly 500,000 pages) for which Mr. Miyazaki was the sender or a recipient were retained in the email files of other employees. (*Id.* at 16; Ex. 25, Vol. VII, 02/10/14 Tr. at 859:22 – 860:4 (Calahan)).

Fourth, it is also undisputed that in 2002 Takeda started making retention tape copies of U.S. employee emails, and that Takeda started using a similar retention tape procedure for EU employee emails in 2005. (*See* Ex. 24, Vol. V, 02/06/14 Tr. at 638:2-7 (Calahan)). Again, any

[41] For example, Dr. Claire Thom – whom Plaintiffs called as an adverse witness in their case-in-chief to testify about Takeda's interactions with the FDA regarding Actos and bladder cancer – remained at Takeda or a Takeda affiliate until 2013, (*See* Ex. 28, Vol. X, 02/13/14 Tr. at 1239:14-17 (Thom)), and Takeda preserved her custodial files and produced them to Plaintiffs. Takeda also preserved the custodial files of some of the other key employees involved with Actos who left Takeda before the summer of 2011. For example, Takeda preserved and produced Dr. Bhattacharya's custodial file. As Dr. Bhattacharya testified (via deposition) at trial, she worked on drug safety issues at Takeda from 2002 to 2008, including the issue of a potential association between Actos and bladder cancer. (*See, e.g.*, Ex. 44, Bhattacharya 1A at 451:11 – 452:4, 454:19 – 485:20).

alleged "cover up" plan would be an ill-conceived one given the existence of those retention tape systems.

Plaintiffs cannot save their punitive damages verdict by arguing that the jury could merely "infer" that missing custodial files contained evidence that Takeda acted in wanton disregard of patient safety. The evidence presented at trial is inconsistent with any inference that the missing files contained some sort of "smoking gun" on whether Actos causes bladder cancer. Plaintiffs' own experts repeatedly told the jury that randomized clinical trial data is the "gold standard" for determining whether a drug causes a disease,[42] and that the next two best forms of evidence on general causation are meta-analyses of randomized clinical trial data and the results of epidemiological studies.[43] Plaintiffs offered no evidence that employee custodial files would contain randomized clinical trial data or epidemiological data not already included in Takeda's filings with the FDA (all of which were provided to Plaintiffs during discovery).[44] And, as is discussed above, the undisputed evidence showed that the FDA determined that the Actos labeling was always appropriate based on the randomized clinical trial data and epidemiological data available at the time.

6. Plaintiffs' demand for punitive damages against Lilly fails for several additional reasons.

Finally, a punitive damages award against Lilly is prohibited for at least three additional reasons.

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[42] (*See, e.g.*, Ex. 30, Vol. XVI, 02/24/14 Tr. at 2315:21-22 (Plaintiffs' expert statistician, Dr. Madigan, testifying: "Randomized trials, everyone agrees, is the gold standard of evidence.") (*See also* Ex. 26, Vol. VIII, 02/11/14 Tr. at 1005:19-25 and Ex. 27, Vol. IX, 02/12/14 Tr. at 1085:4-6 (Dr. Kessler describing randomized clinical trials as the "gold standard" for determining causation)).

[43] (Ex. 31, Vol. XVII, 02/26/14 Tr. at 2422:5 – 2423:18 (Dr. Delacroix testifying that after randomized clinical trials, the next best evidence on the issue of causation is meta-analyses of randomized clinical trials, followed by epidemiological studies)).

[44] As is shown above, a meta-analysis would have made no difference in this case.

First, as noted, Plaintiffs' contended that the omission of bladder cancer from the label demonstrated the requisite "reckless or wanton disregard of [the] safety or rights" of others. *Ross*, 868 N.E.2d at 196. But, as explained above, federal law prevented Lilly from making any changes to Actos' warnings. *See* Part 1, *supra*. Lilly could not have acted with a wanton disregard for the safety of others by failing to make label changes that it was prohibited from making.

Second, Plaintiffs' theory of liability with respect to Lilly was based on Lilly's role as a "co-promoter" of Actos. (ECF Doc. 3817, Summary Judgment Mem. Op. at 9). There is no legal authority to hold a "co-promoter" liable for failure to warn or negligent marketing simply based on its contractual relationship with the holder of the NDA as a co-promoter. But, even if Lilly could be liable as a mere co-promoter – and it cannot (Ex. 3, 12/14/98 Agreement Between Lilly and Takeda, P470 at 10-12) – the Co-Promotion Agreement, as well as Lilly's involvement with Actos' marketing, ended on March 31, 2006. And, as noted above, Lilly's sales representatives' last visits to Mr. Allen's physicians occurred almost two years before Mr. Allen began taking Actos. Lilly's contacts with Mr. Allen's prescribing physicians were so attenuated that the jury lacked sufficient evidence to find any marketing that could have formed the basis of Plaintiffs' negligent marketing claim, much less evidence of misconduct that was "exceptional" and demonstrated a "reckless or wanton disregard of [the] safety or rights" of others. *Ross*, 868 N.E.2d at 196.

Third, even assuming *arguendo* that a finding of spoliation could form the basis of a punitive damages award, punitive damages against Lilly cannot be justified based on such a finding, as no allegations or findings of spoliation were made against Lilly. This Court's

spoliation opinions and findings were limited to Takeda, making no mention whatsoever of any Lilly conduct.

CONCLUSION

For the reasons discussed above, Defendants respectfully request that the Court enter judgment for Defendants on all of Plaintiffs' claims and on Plaintiffs' demand for punitive damages.

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Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on June 27, 2014, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system, which will send a notice of electronic filing to Plaintiffs' Steering Committee, Lead Defense Counsel and Defendants' and Plaintiffs' designees. The designees will forward the NEFs to the appropriate attorneys as outlined by the Court's Case Management Order: Notice of Procedure [D.E. 3398].

/s/ Sara J. Gourley

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