UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PROTON-PUMP INHIBITOR PRODUCTS LIABILITY LITIGATION

2:17-MD-2789 (CCC) (LDW)
(MDL 2789)
and all member and related cases

This Document Relates to:

***Bales v. AstraZeneca Pharmaceuticals LP, et. al.,* No. 2:17-cv-06124**

***Foster v. AstraZeneca Pharmaceuticals LP, et al.,* No. 2:17-cv-02475**

***Kersch v. AstraZeneca Pharmaceuticals LP, et al.,* No. 2:18-cv-03159**

***Lee v. AstraZeneca Pharmaceuticals LP, et al.,* No. 2:17-cv-00212**

***Nelson v. AstraZeneca Pharmaceuticals LP, et al.,* No. 2:17-cv-13727**

***Rieder v. AstraZeneca Pharmaceuticals LP, et al.,* No. 2:19-cv-00850**

Judge Claire C. Cecchi

REPORT & RECOMMENDATION OF SPECIAL MASTER ELLEN K. REISMAN REGARDING DEFENDANTS' PREEMPTION MOTIONS

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I. INTRODUCTION

The Judicial Panel on Multidistrict Litigation ("JPML") established this MDL proceeding in August 2017 to consolidate claims alleging personal injury and wrongful death resulting from the use of proton pump inhibitor ("PPI") drugs. In Case Management Order ("CMO") No. 33, the Court created a process for bellwether selection, and in accordance with CMO No. 36, twenty plaintiffs were identified as those whose cases would be worked up as potential bellwethers.[1] In CMO No. 48, the Court selected six cases as the Bellwether Trial Cases, and the parties have been preparing these cases for trial.[2] Trial in the first bellwether case, *Rieder*, is scheduled to begin on November 14, 2022, with trial in *Foster* scheduled on March 1, 2023, and trial in *Bales* scheduled on April 10, 2023.[3]

AstraZeneca Pharmaceuticals LP and AstraZeneca LP (collectively "AstraZeneca") are defendants in all six of the Bellwether Trial Cases, and Merck Sharp & Dohme Corporation is named as a defendant in the *Rieder* and *Kersch* cases.[4] Takeda Pharmaceuticals Company Limited, Takeda Pharmaceuticals

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[1] CMO No. 33, No. 2:17-md-2789, ECF No. 513; CMO No. 36, No. 2:17-md-2789, ECF No. 548.

[2] CMO No. 48, No. 2:17-md-2789, ECF No. 665. The six cases selected as the Bellwether Trial Cases are: *Freddy Bales*, No. 2:17-cv-06124; *David Foster*, No. 2:17-cv-02475; *Steve Kersch*, No. 2:18-cv-03159; *Kimberly Lee*, No. 2:17-cv-00212; *Diane Nelson*, No. 2:17-cv-13727; and *James Rieder*, No. 2:19-cv-00850.

[3] CMO No. 76, No. 2:17-md-2789, ECF No. 801.

[4] For purposes of this Report and Recommendation ("R&R"), "AstraZeneca" also includes Merck Sharp & Dohme Corporation for those two cases.

America, Inc., Takeda Development Center Americas, Inc. f/k/a Takeda Global Research & Development Center, Inc., and Takeda Pharmaceuticals U.S.A., Inc. (collectively "Takeda") are defendants in *Bales* only.

In CMO No. 50, amended by subsequent CMOs, including CMO Nos. 75 and No. 76, the Court directed me to prepare Reports and Recommendations ("R&R") as to, *inter alia*, motions for summary judgment filed by the parties in the six Bellwether Trial Cases.[5] Among those summary judgment motions are motions by AstraZeneca in the six Bellwether Trial Cases and Takeda in *Bales* seeking partial summary judgment on Plaintiffs' state law failure to warn claims on the ground that they are preempted by federal law.[6] Defendants argue that under the provisions of

[5] *See* CMO No. 50, No. 2:17-md-2789, ECF No. 685; CMO NO. 67, No. 2:17-md-2789, ECF No. 747; CMO No. 75, No. 2:17-md-2789, ECF No. 784, CMO No. 76.

[6] *See* **(1)** AstraZeneca Defendants' Notice of Motion For Summary Judgment On The Grounds That Plaintiffs' State Law Failure-To-Warn Claims Are Preempted By Federal Law, No. 2:19-cv-00850, ECF No. 31; AstraZeneca Defendants' Statement of Undisputed Material Facts In Support of Motion, No. 2:19-cv-00850, ECF No. 31-1 ("AstraZeneca Def. *Rieder* Undisp. Facts"); AstraZeneca Memorandum Of Law In Support Of Motion, No. 2:19-cv-00850, ECF No. 31-2 ("AstraZeneca *Rieder* Preemption Mem."); **(2)** AstraZeneca Defendants' Notice of Motion For Summary Judgment On The Grounds That Plaintiffs' State Law Failure-To-Warn Claims Are Preempted By Federal Law, No. 2:17-cv-06124, ECF No. 73; AstraZeneca Defendants' Statement of Undisputed Material Facts In Support of Motion, No. 2:17-cv-06124, ECF No. 73-1 ("AstraZeneca Def. *Bales* Undisp. Facts"), AstraZeneca Memorandum Of Law In Support Of Motion, No. 2:17-cv-06124, ECF No. 73-2 ("AstraZeneca *Bales* Preemption Mem."); **(3)** Takeda Defendants' Notice of Motion For Partial Summary Judgment On Preemption Grounds, No. 2:17-cv-06124, ECF No. 71, Takeda Defendants' Statement of Undisputed Material Facts In Support of Motion, No. 2:17-cv-06124, ECF No. 71-1 ("Takeda *Bales* Undisp. Facts"), Takeda Memorandum Of Law In Support Of Motion, No. 2:17-cv-06124,

the federal Food, Drug and Cosmetic Act ("FDCA") providing for regulation of pharmaceutical labeling by the U.S. Food and Drug Administration ("FDA"), FDA's implementing regulations, and FDA's labeling decisions regarding PPI drugs, the manufacturers were prohibited from changing their FDA-approved labels to reflect additional warnings of potential kidney injury.[7] Thus, Defendants argue, citing the Supreme Court's decisions in *Merck Sharpe & Dohme Corp. v. Albrecht,* 139 S. Ct. 1668 (2019), and *Wyeth v. Levine,* 555 U.S. 555 (2009), the state law failure to warn claims are preempted under the Supremacy Clause of the U.S. Constitution because it would have been impossible for Defendants to comply with both federal law and any alleged additional state law duty to warn.[8] The Plaintiffs' Steering Committee ("PSC"), on behalf of Plaintiffs in these cases, opposes the motions.[9]

To facilitate the preparation of my R&R on the preemption motions, I requested and on April 5, 2022, heard oral argument via Zoom by counsel for AstraZeneca, Takeda, and the PSC. A copy of the oral argument transcript and certain PowerPoint slides presented by AstraZeneca's counsel are attached as

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ECF No. 71-2 ("Takeda *Bales* Preemption Mem."). The AstraZeneca motions and supporting documents related to *Rieder* and *Bales* address the plaintiffs in all six Bellwether Trial Cases.

[7] *See* AstraZeneca *Rieder* Preemption Mem. 29-40; AstraZeneca *Bales* Preemption Mem. 29-40; Takeda *Bales* Preemption Mem. 20-27.

[8] *See* AstraZeneca *Rieder* Preemption Mem. 29-40; AstraZeneca *Bales* Preemption Mem. 29-40; Takeda *Bales* Preemption Mem. 20-27.

[9] PSC's Brief Opposing Defendants' Motions for Summary Judgment On Failure-to-Warn Preemption, ECF No. 728 ("PSC Opp. Mem.").

Exhibit 1 to this R&R. Thereafter, the parties were ordered in CMO No. 75 to provide supplemental briefing addressing certain issues, including but not limited to the recent decision of the United States District Court for the District of New Jersey on remand from the Supreme Court and the U.S. Court of Appeals for the Third Circuit in the *Merck v. Albrecht* case.[10] Those supplemental submissions were received on May 31 and June 8, 2022.[11]

After a careful review of the voluminous record, I recommend that Defendants' motions be denied for the reasons set forth below.

II. PLAINTIFFS' FAILURE TO WARN CLAIMS

A Master Long Form Complaint ("Master Complaint") was filed in MDL 2789 that allows individual plaintiffs to incorporate relevant allegations and causes of action by reference in their individual short form complaints.[12] The Master Complaint alleges that PPIs cause a variety of serious kidney injuries, including Acute Interstitial Nephritis ("AIN"), Acute Kidney Injury ("AKI"), End-Stage Renal Disease ("ESRD") and Chronic Kidney Disease ("CKD").[13] Count III, Failure to

[10] CMO No. 75 (Setting deadlines for submissions and a revised schedule for issuance of an R&R and any appeal process).
[11] Brief extensions of the time limits in CMO No. 75 were granted.
[12] Pls.' Master Long Form Compl. and Jury Demand, ECF No. 118 ("Master Complaint").
[13] Master Complaint ¶¶ 179-211. "Consumers, including Plaintiffs, who have used Defendants' PPI Products have suffered from severe kidney injuries including, but not limited to, AIN, AKI, CKD and ESRD." Master Complaint ¶ 226.

Warn, alleges that "Defendants had a duty to warn Plaintiffs and their healthcare providers regarding the risks associated with ingesting PPI Products and failed to warn of the risk of kidney injuries that may be irreversible, permanently disabling and life-threatening."[14] It further alleges that "Plaintiffs and/or Plaintiffs [sic] healthcare providers were unaware, and could not have reasonably known or have learned through reasonable diligence, that Plaintiffs had been exposed to the risks identified in this Master Long Form Complaint."[15] It alleges that, had such warnings been provided, Plaintiffs and their physicians would have been on notice of the risks, so that "they would not have used [PPI Products] or they would have altered the frequency or duration of use."[16] And it alleges that, as a result of the absence of

[14] Master Complaint ¶ 325; *see also* Master Complaint ¶¶ 327 ("Defendants failed to provide adequate warnings or instructions that a manufacturer exercising reasonable care would have provided concerning the risk of kidney injury that may be irreversible, permanently disabling and life-threatening in light of the likelihood that the PPI Products would cause these injuries."), 343 ("The warnings that were given by the Defendants failed to properly warn physicians and/or other healthcare providers, including those of the Plaintiffs, of the risks associated with Defendants' PPI Products, thereby subjecting patients, including the Plaintiffs, to unreasonable and foreseeable risks that exceeded the purported and marketed benefits of Defendants' PPI Products."); PSC. Stmt. Of Undisp. Facts ¶¶ 7, 50 (Complaint alleges that labels should have contained warnings of a risk of "permanent or chronic renal injury" or potential "permanent and irreversible renal injuries."); Oral Args. 40:6-12, Apr. 5, 2022, attached hereto in pertinent part as Ex. 1. (Mr. Autry: "There were no warnings in Takeda's label at the time about any possible harm to Bales' kidneys, zero, at the time that Bales took Prevacid. . . . Dr. Fowler said that if he had known about the risk of kidney injuries, he would not have recommended PPIs to Mr. Bales."); Oral Args. 42:8-25, 43:1-13, Apr. 5, 2022.

[15] Master Complaint ¶ 231; *see also* Master Complaint ¶¶ 333, 343.

[16] Master Complaint ¶ 338; *see also* Master Complaint ¶¶ 344-48.

adequate warnings, "Plaintiffs were caused to suffer serious and dangerous side effects, including serious kidney injuries and other severe and personal injuries (in some cases death), which are permanent and lasting in nature, physical pain and mental anguish, diminished enjoyment of life and financial expenses for hospitalization and medical care."[17]

Four of the six Bellwether Trial Case Plaintiffs (*Rieder*, *Bales*, *Foster*, and *Kersch*) incorporate by reference in a Short Form Complaint the allegations of the Master Complaint and each alleges, among other claims, a failure to warn claim.[18] The Complaints in the *Lee* and *Nelson* cases, like the Master Complaint, allege that

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[17] Master Complaint ¶ 348.

[18] *See*, *e.g.*, Second Am. Short Form Compl. 1, 5-6, No. 19-cv-00850, ECF No. 1 ("*Rieder* Second Am. Compl.").

I note that, in addition to their failure to warn claims, Plaintiffs in the six Bellwether Trial Cases also assert other state law claims related to alleged misrepresentations, breaches of warranty, and fraudulent concealment by Defendants AstraZeneca and Takeda. *See* Master Complaint Counts VI, VII, VIII, IX, X; *infra* n.18 (incorporations by reference in short form complaints). AstraZeneca's and Takeda's motions for partial summary judgment on preemption grounds address only the failure to warn claims, not those other claims. *See* motions cited in n.6, *supra*; Oral Args. 67:22-68:10, Apr. 5, 2022. At oral argument, in response to my question noting that the preemption motions did not address these other causes of action, counsel for AstraZeneca argued that "to the degree any of those claims are based on the labeling and the content of the label, they would be preempted as well," but to the extent they asserted independent claims, they would not be. *See* Oral Args. 68:11-69:2, Apr. 5, 2022. Given my recommendation that the motion for summary judgment on preemption grounds with respect to the failure to warn claims should be denied, and AstraZeneca's counsel's position that those claims should be treated similarly to the extent they rely on the warnings in the labels, I need not address those claims specifically or whether any preemption argument as them has been waived.

PPIs can cause a variety of serious kidney injuries, including among others AIN, CKD, and AKI, and that the Nexium label failed to warn adequately of the risks of kidney injury.[19]

1. James Rieder

Plaintiff James Rieder used Nexium, which was marketed by AstraZeneca, to treat gastroesophageal reflux disease ("GERD") between 2002 and 2015.[20] In his complaint against AstraZeneca, Plaintiff Rieder alleges that Nexium use was a cause of his chronic kidney disease ("CKD").[21] The complaint in *Rieder* asserts a failure to warn claim under Ohio law (among other claims).[22]

2. Freddy Bales

Plaintiff Freddy Bales used Nexium to treat GERD between November 2007 and April 2016.[23] Plaintiff Bales alleges that Nexium use was a cause of his CKD,

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[19] *See* Complaint ¶¶ 24-47, Count II, *Lee v. AstraZeneca Pharms. LP, et al.*, No. 2:17-cv-00212, ECF No. 1 ("*Lee* Compl."); Complaint ¶¶ 40-58, Count II, *Nelson v. AstraZeneca Pharms. LP, et al.*, No. 2:17-cv-13727, ECF No. 1 ("*Nelson* Compl.").

[20] *Rieder* Second Am. Compl. ¶¶ 10–11**;** *see also* Plaintiff Steering Committee's Proposed Statement of Facts and Conclusions of Law ("PSC Supp. SOF-COL") ¶ 10, ECF No. 791.

[21] *Rieder* Second Am. Compl. ¶ 11; s*ee also* Derek M. Fine Report 8, Hindy Cert. I, Ex. O ("It is my opinion with reasonable medical and scientific certainty that Mr. Rieder's long-term use of PPIs (in this case Nexium) was a substantial factor to his developing chronic kidney disease . . . ."), ECF No. 73-18; PSC Supp. SOF-COL ¶ 1. (Unless otherwise indicated herein, "Hindy Cert." refers to the certification of exhibits in support of AstraZeneca's preemption motion filed in No. 2:17-cv-06124.)

[22] *See Rieder* Second Am. Compl. ¶ 14; PSC Supp. SOF-COL ¶ 1.

[23] *See* Pl. Bales' Second Am. Fact Sheet 10, Hindy Cert. I, Ex. C, ECF No. 73-6.

which his physician diagnosed in June 2015.[24] He asserts a state law failure to warn claim against AstraZeneca (among other claims).[25]

Plaintiff Bales also asserts a state law failure to warn claim against Takeda, which manufactured and sold the Prevacid that Plaintiff Bales used from April 2005 to September 2007 prior to switching to Nexium.[26] He alleges that his Prevacid use was also a cause of his CKD.[27]

3. David Foster

Plaintiff's Decedent David Foster used Nexium, which was marketed by AstraZeneca, to treat GERD between February 2010 and October 2014, and Angel Maria Lee, the Administrator of David Foster's Estate, alleges that it was a cause of David Foster's CKD and caused his death.[28] The complaint in *Foster* asserts a state law failure to warn claim (among other claims).[29]

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[24] *See* Pl. Bales' Second Am. Fact Sheet 12–13; Second Am. Short Form Compl. ¶ 11, *Bales v. AstraZeneca Pharms. LP*, No. 17-cv-06124, ECF No. 42 ("*Bales* Compl."); *see also* David R. Powers Report (*Bales*) 10, Hindy Cert. I, Ex. E ("[I]t is my opinion with reasonable medical certainty that PPIs were the cause of Mr. Bales' chronic kidney disease."), ECF No. 73-8.

[25] *See Bales* Compl. ¶¶ 13-14.

[26] *See* Takeda *Bales* Undisp. Facts ¶ 3; *Bales* Compl. ¶¶ 5, 10, 11, 14; PSC Supp. FOF-COL ¶ 5.

[27] *Bales* Compl. ¶¶ 5, 10, 11.

[28] *See* AstraZeneca Defendants Proposed Findings of Fact and Conclusions of Law ¶ 24, No. 2:19-cv-00850, ECF. No. 59-1 ("AstraZeneca Supp. Proposed FOF-COL"); Pl. Supp. FOF-COL ¶ 6; Third Am. Short Form Compl. and Jury Demand ¶¶ 4, 11, *Foster v. AstraZeneca Pharms. LP, et al.*, No. 2:17-cv-02475, ECF No. 83 ("Foster Am. Compl.").

[29] *See* Foster Am. Compl. ¶ 14, Count III.

4. Steven Kersch

Plaintiff Steven Kersch used Nexium, which was marketed by AstraZeneca, to treat GERD between February 2010 and October 2018.[30] In his complaint, Plaintiff Kersch alleges that Nexium use was a cause of his CKD and AKI.[31] The *Kersch* complaint asserts a state law failure to warn claim (among other claims).[32]

5. Kimberly Lee

Plaintiff Kimberly Lee used Nexium, which was marketed by AstraZeneca, to treat GERD between July 2010 and at least October 2014.[33] In her complaint, Plaintiff Lee alleges that Nexium use was a cause of her CKD.[34] The *Lee* complaint asserts a state law failure to warn claim (among other claims).[35]

6. Diane Nelson

Plaintiff Diane Nelson used Nexium, which was marketed by AstraZeneca, to treat GERD between March 2007 and February 2016.[36] In her complaint, Plaintiff

[30] *See* PSC Supp. SOF-COL ¶ 7; AstraZeneca Supp. FOF-COL ¶ 100.
[31] Short Form Compl. And Jury Demand 1, 3, 6-7, *Kersch v. AstraZeneca Pharms. LP, et al.*, No. 2:18-cv-03159, ECF No. 1 ("*Kersch* Compl.").
[32] *Kersch* Compl. ¶ 14.
[33] *See* PSC Supp. SOF-COL ¶ 8; AstraZeneca Supp. FOF-COL ¶ 101.
[34] *See* PSC Supp. SOF-COL ¶ 8; AstraZeneca Supp. FOF-COL ¶ 101; *Lee* Compl. ¶ 1.
[35] *Lee* Compl. Count II.
[36] *See* PSC Supp. SOF-COL ¶ 9; AstraZeneca Supp. FOF-COL ¶ 102.

Nelson alleges that Nexium use was a cause of her CKD.[37] The *Nelson* complaint asserts a failure to warn claim (among other claims).[38]

III. OVERVIEW OF FEDERAL REGULATION OF PHARMACEUTICAL SAFETY AND LABELING

The federal FDCA establishes a regulatory regime designed to ensure that every prescription drug on the market is "safe for use under the conditions prescribed, recommended, or suggested" in its "labeling."[39] Under the FDCA, drug manufacturers bear "ultimate responsibility" for appropriately labeling drugs, including to warn of safety risks.[40] However, the FDCA also requires manufacturers to work with FDA to develop an appropriate label when they submit a new drug for approval.[41] FDA closely regulates the safety information on drug labels.[42] It is a violation of federal law for a manufacturer to distribute a drug that is not labeled in compliance with FDA regulations.[43]

Drug labels include two sections relevant to this case: a "Warnings and Precautions" section and an "Adverse Reactions" section.[44]

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[37] *See* PSC Supp. SOF-COL ¶ 9; AstraZeneca Supp. FOF-COL ¶ 102; *Nelson* Compl. ¶ 69.
[38] *Nelson* Compl. Count II.
[39] 21 U.S.C. § 355(d).
[40] *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).
[41] 21 U.S.C. §§ 355(a), (b), (d)(7); 21 C.F.R. § 314.125(b)(6).
[42] 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 201.57(a).
[43] *See generally Wyeth v. Levine*, 555 U.S. at 571; 21 C.F.R. § 201.57.
[44] *See* 21 C.F.R. §§ 201.57(a)(10) ("Warnings and precautions"), 201.57(a)(11)

The Warnings and Precautions section is required to "include[e] information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm."[45] It must

> describe clinically significant adverse reactions, (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class . . .), limitations on use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section.[46]

Thus, the Warnings and Precautions section of the label identifies a "discrete set" of serious risks that would affect a doctor's prescribing decisions or be "potentially fatal."[47] FDA regulations provide that "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 definitely established."[48]

("Adverse reactions").

[45] 21 C.F.R. § 201.57(a)(10).

[46] 21 C.F.R. § 201.57(c)(6)(i).

[47] 71 Fed. Reg. 3922-01, 3946; FDA, Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, at 3 (Oct. 2011).

[48] 21 C.F.R. § 201.57(c)(6)(i).

FDA regulations regarding the Adverse Reactions section of a drug label require a description of "the overall . . . profile of the drug based on the entire safety database," including a list of all "undesirable effect[s], reasonably associated with use."[49] Given its broader scope, the threshold for warning of an adverse event in the Adverse Reactions section is comparatively lower: there must be "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[50]

FDA regulations also impose a duty on manufacturers authorized to market a drug to perform continuous surveillance of post-marketing adverse events and medical literature, among other sources, to monitor the safety of their products.[51] Moreover, the manufacturer is required to report this information to FDA pursuant to FDA regulations and guidance.[52]

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[49] 21 C.F.R. § 201.57(c)(7).
[50] 21 C.F.R. § 201.57(c)(7).
[51] 21 C.F.R. § 314.80(b).
[52] *See* 21 C.F.R. §§ 314.80, 314.81, 201.57. An adverse drug experience that "is both serious and unexpected, whether foreign or domestic," must be reported "as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant" or other entity (manufacturer, packer or distributor) whose name appears on the label. 21 C.F.R. §§ 314.80(c)(1)(i), (iii). Prompt investigation and follow up reporting regarding such 15-day Alert reports also is required. 21 C.F.R. §§ 314.80(c)(1)(ii), (iii). Other adverse drug experiences must be reported quarterly for three years from the date of approval of the application, and annually thereafter, unless FDA reimposes the quarterly reporting requirement or other reporting schedule. 21 C.F.R. § 314.80(c)(2)(a).

New information about a drug may require changing its label.[53] A drug manufacturer may change its FDA-approved label in one of two ways. The typical way is for the manufacturer to seek advance permission from FDA to make a label change through a Prior Approval Supplement Application ("PAS").[54] If the manufacturer seeks such advance permission, it may not change the label until and unless it receives FDA approval.[55]

"Alternatively, a manufacturer may change a label immediately and unilaterally through an exception to the normal advance FDA approval process – a Changes Being Effected Application ('CBE') to reflect 'newly acquired information' about 'evidence of a causal association between the drug and a risk of harm.'"[56] "Newly acquired information" means risks not previously known or previously underestimated.[57] In particular, "newly acquired information" includes

> data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events,

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[53] *See* 21 C.F.R. §§ 314.70(b)(ii)(v)(C), 314.70(c)(6)(iii), 314.81(b)(2)(i); *Merck v. Albrecht*, 139 S. Ct. at 830; *In re Fosamax Alendronate Sodium Prods. Liab. Litig.*, 2022 U.S. Dist. LEXIS 52627, at *38 (D. N.J. Mar. 23, 2022) ("*Fosamax*").
[54] *See* 21 C.F.R. §§ 314.70(b)(ii)(v)(C), 314.70(c)(6)(iii); *Fosamax*, 2022 U.S. Dist. LEXIS 52627, at *39.
[55] 21 C.F.R. §§ 314.70(b)(2)(v)(A), (b)(4).
[56] *Fosamax*, 2022 U.S. Dist. LEXIS 52627, at *39 (citing 21 U.S.C. §§ 314.70(c)(6)(iii)(A) (CBE regulation), 314.3(b) (defining "newly acquired information")).
[57] 21 C.F.R. § 314.3(b).

> or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.[58]

When a manufacturer changes a label through the CBE process, it can use the modified label after notifying FDA but before FDA completes its review of the change. If FDA subsequently rejects a labeling change implemented by the manufacturer, the manufacturer must cease using it.[59]

Whichever method a manufacturer chooses to modify a label, any modification to the Warnings and Precautions section or the Adverse Reactions section must meet the relevant causal thresholds described above for inclusion in that section.[60]

IV. OVERVIEW OF RELEVANT LABELING HISTORY

A. Initial Nexium Labeling

Nexium is the brand name for esomeprazole magnesium, a PPI manufactured by AstraZeneca that was approved by FDA for marketing in the United States on February 20, 2001.[61] The original Nexium label did not contain any information in either the Warnings and Precautions section or the Adverse Reactions section about

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[58] 21 C.F.R. § 314.3(b); *see also Wyeth v. Levine*, 555 U.S. at 569.
[59] *See Wyeth v. Levine*, 555 U.S. at 571.
[60] 21 C.F.R. §§ 201.57(e), 201.80(e).
[61] PSC Supp. FOF-COL ¶ 2; *see also* AstraZeneca Defendants' Proposed Findings Of Fact And Conclusions Of Law ¶ 12, No. 2:17-cv-06124, ECF No. 111-1 ("AstraZeneca Supp. FOF-COL").

kidney conditions observed in patients taking the drug; however, in the Adverse Reactions section, the Nexium label did cross-reference the label of omeprazole (Prilosec) – another PPI drug that is a "racemate" (close chemical relative) of esomeprazole (Nexium) – stating that "[o]ther adverse events not observed with NEXIUM but occurring with omeprazole can be found in the omeprazole package insert, ADVERSE REACTIONS section."[62] The omeprazole ADVERSE REACTIONS section listed interstitial nephritis as an adverse reaction that had been observed.[63]

B. Initial Prevacid Labeling

Prevacid is the brand name for lansoprazole, a PPI manufactured by Takeda that was approved by the FDA for marketing in the United States on May 10, 1995.[64] As with Nexium, as of 2001, Prevacid's labeling did not include any reference in the Warnings and Precautions section or Adverse Reactions section of the label to kidney conditions observed in patients taking the drug.[65]

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[62] AstraZeneca Supp. FOF-COL ¶ 14 (quoting Feb. 2001 Nexium label at 22, copy submitted as Hindy Cert., Ex. Q, ECF No. 73-20).
[63] *See* AstraZeneca Supp. FOF-COL ¶¶ 5-8.
[64] *See* PSC Supp. SOF-COL ¶ 3; Takeda Def. L. R. 56.1 Statement of Undisputed Material Facts in Support of Motion for Partial Summary Judgment ¶ 12.
[65] *See* Letter dated May 3, 2001 from L. Talarico, M.D., Director, Div. of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research, FDA and related correspondence to TAP Pharmaceutical Products, Inc. enclosing approved text for Prevacid label, at 23, 28 (copy attached as Ex. J to Anderson Cert., No. 2:17-cv-06124, ECF No. 71-13).

C. Post-Marketing Reports and 2006/2007 Amendments Of The Adverse Reactions Sections Of The Nexium and Prevacid Labels To Add Interstitial Nephritis

During the period after Nexium and Prevacid were initially approved by FDA, various adverse event reports, case studies, and other publications reported kidney-related conditions among users of PPIs, including but not limited to reports of interstitial nephritis.[66] These included, among other case reports and case series:

- Delve (2003), a case study of two women who suffered progressive renal failure due to acute tubulointerstitial nephritis ("AIN" or "ATIN"), which also discussed 11 cases of AIN in PPI patients reported in New Zealand and reviewed published literature;[67]
- Ra and Tobe (2004), a case report regarding AIN in a patient using the PPI pantoprazole;[68]

[66] *See* PSC Supp. FOF-COL ¶¶ 39-45; AstraZeneca Supp. FOF-COL ¶ 15; Takeda Defendants' Proposed Findings Of Fact And Conclusions Of Law In Support Of Its Motion For Partial Summary Judgment On Preemption Grounds ¶¶ 34-36, No. 2:17-cv-06124, ECF No. 109 ("Takeda Supp. FOF-COL").

[67] *See* PSC Supp. FOF-COL ¶ 39, PSC Opp. Ex. 29 (Peter Delve, et al., "*Omeprazole-Induced Acute Interstitial Nephritis*," The New Zealand Medical Journal (Online) 116, no. 1169 (2003)); *see also* Takeda Supp. FOF-COL ¶ 33 (noting 2006 submission to FDA of Delve).

[68] *See* PSC Supp. FOF-COL ¶ 41, PSC Opp. Ex. 19 (Amy Ra and Sheldon W. Tobe, "*Acute Interstitial Nephritis Due to Pantoprazole*," Annals of Pharmacotherapy 38, no. 1 (2004)); AstraZeneca's Response To PSC Supp. FOF-COL App. A at 3 (noting no dispute regarding submission to FDA).

- Yamamoto (2004), a case report of a patient who developed renal insufficiency after taking the PPI lansoprazole, experienced improved renal function on discontinuation, experienced renal function deterioration when started on another PPI, and ultimately was diagnosed with acute renal failure and AIN;[69]
- Torpey (2004), a published case series analyzing renal biopsy results from 296 patients that found an association between AIN and the PPIs omeprazole and lansoprazole in one-third of the cases, noted that many patients stabilized after withdrawal of PPI, and that many patients did not present with traditional symptoms of AIN;[70] and
- Geevasinga (2005), reporting AIN in two patients using Nexium, one of whom ultimately developed renal failure and the other of whom

[69] *See* PSC Supp. FOF-COL ¶ 41, PSC Opp. Ex. 18; AstraZeneca's Response To PSC Supp. FOF-COL App. A at 3 (noting report to FDA in AstraZeneca 2005 Post-Marketing Safety Update Report); Takeda Supp. FOF-COL ¶¶ 31-32 (noting 2004 Takeda submissions to FDA).

[70] *See* PSC Supp. FOF-COL ¶ 43, PSC Opp. Ex. 31 (N. Torpey, T. Barker, and C. Ross, "*Drug-Induced Tubulo-Interstitial Nephritis Secondary to Proton Pump Inhibitors: Experience from a Single UK Renal Unit*," Nephrology Dialysis Transplantation 19, no. 6 (June 1, 2004): 1441-46); AstraZeneca's Response To PSC FOF-COL App. A at 3 (noting FDA awareness of Torpey, which is cited in 2005 Postmarketing Safety Review, Hindy Cert. I Ex. CC at 2, ECF No. 73-34); Takeda Supp. FOF-COL ¶ 33 (noting reference to Torpey in 2005 Takeda Prevacid Annual Report submission to FDA).

developed end-stage renal disease, which the authors noted could be downstream consequences of AIN.[71]

In April 2005, after reviewing post-marketing adverse event reports and medical literature regarding interstitial nephritis associated with PPI use, FDA's Office of Safety and Epidemiology prepared a post-marketing safety review.[72] The review specifically referenced Torpey and Geevasinga (2005) and "79 reports, 10 reports, and 22 reports of interstitial nephritis for PPIs esomeprazole, rabeprazole, and pantoprazole, respectively . . .."[73] It noted that only three of five PPIs on the market listed interstitial nephritis in the label as a post-marketing reported event and recommended class labeling for all PPIs regarding interstitial nephritis.[74]

On March 16, 2006, after reviewing post-marketing adverse event reports associated with Nexium, AstraZeneca notified FDA that it intended to modify the Adverse Reactions section of the Nexium label to include "interstitial nephritis."[75]

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[71] *See* PSC Supp. FOF-COL ¶ 45, PSC Opp. Ex. 32 (Nimeshan Geevasinga et al., "*Acute Interstitial Nephritis Secondary to Esomeprazole*," The Medical Journal of Australia 182, no. 5 (2005): 235-36 ("Geevasinga (2005)"); AstraZeneca's Response To PSC FOF-COL App. A at 4 (AstraZeneca disclosed to FDA).
[72] *See* PSC Supp. FOF-COL ¶ 47, Ex. 226; AstraZeneca Supp. FOF-COL ¶ 17.
[73] *See* Takeda Supp. FOF-COL ¶ 35 (quoting FDA review); *see also* PSC Supp. FOF-COL ¶ 48.
[74] *See* PSC Supp. FOF-COL ¶ 47, PSC Opp. Ex. 226; Takeda Supp. FOF-COL ¶ 36.
[75] *See* AstraZeneca Supp. Proposed FOF-COL ¶ 18 (citing Nexium Special Supplement CBE, copy attached as Hindy Cert. I, Ex. AA, ECF No. 73-72).

Although AstraZeneca styled its request as a CBE, it also stated that it did not intend to implement the proposed label change until after receiving FDA approval.[76]

In September 2006, FDA approved modification of the Adverse Reactions section of the Nexium labeling to read as follows:

> Postmarketing Reports – There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports occurred rarely and are listed below by body system: . . . ***Renal and Urinary Disorders***: interstitial nephritis.[77]

No change was proposed by AstraZeneca or made to the Warnings and Precautions section of the Nexium label.

On July 31, 2006, FDA requested that "interstitial nephritis" be added to the "postmarketing . . . urogenital system" section of the Prevacid labeling under the Adverse Reactions section.[78] Takeda filed a CBE to that affect, which FDA approved on June 20, 2007.[79] Takeda, like AstraZeneca, did not propose or make

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[76] *See* Nexium Special Supplement CBE, copy attached as Hindy Cert. I, Ex. AA; *see also* AstraZeneca Preemption Mem. 17-19 and exhibits cited therein.

[77] *See* Letter from Joyce Korvick, M.D., M.P.H., Deputy Dir., Div. of Gastroenterology Prods., Center for Drug Evaluation and Research, to George A. Kummeth, Dir., Regulatory Affairs (Sept. 15, 2006), Hindy Cert. I, Ex. DD; AstraZeneca, *Nexium* Label (Sept. 15, 2006), Hindy Cert. I, Ex. EE, at 21.

[78] *See* Letter from J. Korvick, FDA to TAP Pharmaceutical Products Inc. (July 31, 2006), copy attached as Anderson Cert. Ex. L, No. 2:17-cv-06124, ECF No. 71-18; Takeda *Bales* Undisp. Facts ¶ 19.

[79] *See* Takeda *Bales* Undisp. Facts ¶ 20; Anderson Cert. Ex. M, No. 2:17-cv-06124, ECF No. 71-19.

any change in its 2006 CBE to the Warnings and Precautions section of the Prevacid labeling.

D. Publication Of Additional Data, The 2011 Citizen's Petition, And The 2014 Amendment Of The Warnings and Precautions Section Of PPI Labels To Include "Acute Interstitial Nephritis"

Additional data continued to be generated concerning post-marketing kidney related adverse events in patients taking PPIs. A May 2006 Geevasinga article was submitted to FDA in May 2007 in AstraZeneca's annual Periodic Safety Update Report ("PSUR") for Nexium's racemate omeprazole (Prilosec) for the period April 2006-April 2007.[80] The 2006 Geevasinga article was a retrospective case review that found 18 cases of biopsy-proven, PPI-induced acute renal failure. The authors observed that while "[m]ost patients diagnosed with AIN recover renal function . . . some patients retain a degree of renal impairment, and some even progress to end-stage chronic kidney disease (CKD)."[81] Additionally, an article by Simpson published on September 29, 2006 was a case series of 15 cases in New Zealand, many of which involved asymptomatic patients subsequently diagnosed with AIN,

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[80] *See* PSC Supp. FOF-COL ¶¶ 53-54 (citing PSC Opp. Ex. 37, 357-60), Ex. 37 (AstraZeneca Periodic Safety Update, 23 May 2007, AZ-KID-01735387); Takeda Supp. FOF-COL ¶ 4 (stating that "FDA was informed of and addressed Geevasinga (2006) in conjunction with Simpson in 2014 and 2018."). The article, which was published in May 2006, is N. Geevasinga, *et al.*, "*Proton Pump Inhibitors and Acute Interstitial Nephritis*," Clinical Gastroenterology and Hepatology 2006; 4: 597-604, copy available at https://pubmed.ncbi.nlm.nih.gov/16630752/ (last visited July 31, 2022) ("Geevasinga (2006)").

[81] PSC Supp. FOF-COL ¶ 51 (quoting Geevasinga (2006)), PSC Opp. Ex. 35).

some of whom did not recover complete renal function.[82] The 2006 Simpson article was also included in AstraZeneca's PSUR for omeprazole in May 2007.[83] AstraZeneca's PSUR for Nexium (esomeprazole) itself for the March 2006-March 2007 period did not report either the 2006 Geevasinga or Simpson articles.[84] Nor were the articles discussed in the relevant Prevacid (lansoprazole) PSUR submitted in June 2006 and December 2006 by Takeda.[85]

In 2011, Public Citizen filed a Citizen's Petition with FDA requesting, among other things, that PPI labels be amended to reflect the literature associating PPIs with AIN, as well as a review by FDA of the issue.[86] The Citizen's Petition referred to literature published over the past several years and requested that PPI labels be amended on a class basis to reflect the risk of AIN:

> *Acute interstitial nephritis*: Information regarding the potential for drug-induced acute interstitial nephritis, seen in at least 60 case reports, should be included in the appropriate section.[87]

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[82] PSC Supp. FOF-COL ¶ 52 (citing Simpson et al., *Proton Pump Inhibitors and Acute Interstitial Nephritis*, Nephrology 2006; 11, 381-85, PSC Opp. Ex. 36).
[83] *See* PSC Supp. FOF-COL ¶¶ 53-54 (citing PSC Opp. Ex. 37, 357-60), Ex. 37 (AstraZeneca Periodic Safety Update, 23 May 2007, AZ-KID-01735387); Takeda Supp. FOF-COL ¶ 4 (stating that "FDA was informed of and addressed Geevasinga (2006) in conjunction with Simpson in 2014 and 2018.")
[84] *See* PSC Supp. FOF-COL ¶ 54, Ex. 357-58.
[85] *See* PSC Supp. FOF-COL ¶ 54, Ex. 359-60.
[86] AstraZeneca *Rieder* Preemption Mem. 20; Citizen's Pet. from Eric Nellis, Researcher, Public Citizen's Health Research Group et al., to Margaret A. Hamburg, M.D., Comm'r, FDA (Aug. 23, 2011) ("Citizen's Petition") 15-16, Hindy Cert. I, Ex. FF, ECF No. 73-37.
[87] Citizen's Petition 3; *see also* Citizen's Petition 15-16.

In support of this request, the Citizen's Petition focused on the potential for severe and possibly permanent injury resulting from PPI-induced AIN. It stated that

> one-third of the subjects required corticosteroid therapy, and three patients required dialysis, with one remaining on dialysis permanently. Thus, the potential for severe sequelae following AIN [ATIN] possibly induced by PPI use necessitates proper alerting of patients and provider to this serious adverse effect.[88]

After evaluating the relevant literature and data, FDA's Center for Drug Evaluation and Research ("CDER") similarly concluded that

> Untreated drug associated AIN may cause acute renal insufficiency or failure. Treatment of drug induced AIN requires identifying and discontinuing the offending agent. Severe cases may require treatment with steroids or dialysis.[89]

Thus, CDER concluded "increased patient and healthcare provider awareness of AIN with PPIs use may facilitate more rapid diagnosis and management of this serious but potentially reversible condition."[90]

Thereafter, in October 2014, FDA issued a Safety Labeling Change Notification requiring amendment of the Warnings and Precautions sections of all PPI labels to warn of AIN risk.[91] The new language required by FDA in the

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[88] Citizen's Petition 15.

[89] Mem. from Joyce Korvick, M.D., M.P.H. to Emily C. Helms Williams version dated Sept. 26, 2014 ("2014 CDER Review") 22-23 (PSC Supp. Opp. Ex. 376).

[90] 2014 CDER Review 22.

[91] Letter from Joyce Korvick, M.D., M.P.H. to Takeda Pharmaceuticals dated Oct. 30, 2014, copy attached at No. 2:17-cv-06124, ECF No. 71-23; Letter from Joyce Korvick, M.D., M.P.H. to AstraZeneca LP dated Oct. 30, 2014, copy attached as PSC Opp. Ex. Hindy Cert. Ex. 242. *See also* PSC Supp. FOF-COL ¶ 12 (citing

Warnings and Precautions section of the labeling implemented by AstraZeneca and Takeda (and other PPI manufacturers) read:

> Acute interstitial nephritis has been observed in patients taking PPIs including [PPI] Acute interstitial nephritis may occur at any time during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue [PPI]if acute interstitial nephritis develops.[92]

E. FDA Review Of Additional, Subsequent Literature And Other Information Regarding Potential Renal Injury From PPI Use And The 2020 PPI Class Label Amendment

Additional studies and reports continued to be published after the 2014 label change regarding kidney-related adverse events occurring in patients taking PPIs.[93] These included a 2015 Antoniou population-based cohort study of 290,592 individuals that showed a more than two-fold risk of hospitalization for acute kidney injury in patients taking PPIs compared to non-users, and a three-fold risk for AIN in PPI users compared to non-users.[94] They also included 2016 studies by Lazarus

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Takeda Defendants' Statements of Fact and Plaintiffs' Responses to Takeda's Statements of Fact ¶¶ 17-19, AstraZeneca Defendants' Statements of Fact and Plaintiffs' Responses to AstraZeneca's Statements of Fact ¶¶ 35-36); AstraZeneca *Rieder* Preemption Mem. 21 (regarding class label requirement for Warnings and Precautions section of label).

[92] *See* AstraZeneca *Rieder* Preemption Mem. 21 (citing AstraZeneca, *Nexium* Label (Dec. 19, 2014); Hindy Cert. I, Ex. II, § 5.3, ECF No. 73-40).

[93] *See* PSC Supp. FOF-COL ¶¶ 72-77 (citing studies attached as exhibits to PSC Opp.).

[94] *See* PSC Supp. FOF-COL ¶ 72 & PSC Opp. Ex 48 (T. Antoniou et al., "*Proton Pump Inhibitors and the Risk of Acute Kidney Injury in Older Patients: A Population-Based Cohort Study*," CMAJ Open 3, no. 2 (Apr. 16, 2005)).

and Xie that found an increased risk of CKD associated with PPI use.[95] Multiple additional reports were published after 2016 through 2020.[96]

In response to these newly published data, starting in 2016 FDA identified a potential safety signal for CKD, and requested its Division of Epidemiology I ("DEPI") to prepare memoranda addressing the studies.[97] Thereafter, FDA opened a Tracked Safety Issue ("TSI") in April 2017 to consider CKD and AKI in connection with PPI use.[98] FDA's DEPI continued to study the issue and ultimately identified three potential options for FDA action: (1) requiring additional evidence before changing FDA labels for PPI class drugs; (2) adding CKD as a discrete adverse reaction to the Warnings and Precautions section of labels for PPI class drugs; and (3) clarifying information about AIN in the Warnings and Precautions section of PPI class drug labels.[99]

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[95] *See* PSC Supp. FOF-COL ¶¶ 74-75; *see also* PSC Opp. Exs. 49 (Benjamin Lazarus et al., "Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease," JAMA Internal Medicine 176, no. 2 (Feb. 1, 2016): 238), 50 (Yan Xie et al., "Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD," Journal of the American Society of Nephrology 27, no. 10 (Oct. 2016): 3153-63).

[96] *See* PSC Supp. FOF-COL ¶¶ 76-77; AstraZeneca Supp. FOF-COL ¶ 41 (noting FDA Division of Epidemiology I review of 12 articles, published in 2016 or later, and other studies regarding PPIs and kidney disease).

[97] *See* AstraZeneca Supp. FOF-COL ¶¶ 29-37; PSC Supp. FOF-COL ¶¶ 79-82.

[98] *See* AstraZeneca Supp. FOF-COL ¶¶ 38, 40.

[99] *See* AstraZeneca Supp. FOF-COL ¶¶ 44-48.

On June 18, 2020, FDA proposed a class labeling change for all PPIs, including Nexium and Prevacid, regarding tubulointerstitial nephritis ("TIN").[100] FDA proposed the following PPI class labeling language ("2020 Proposed PPI Class Labeling Revision"):

> Tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Presentation ranges from symptomatic acute hypersensitivity reactions to an asymptomatic gradual reduction in glomerular filtration rate. In reported case series, TIN was diagnosed on biopsy and in the absence of extra-renal manifestations of systemic inflammatory symptoms up to two years after the start of PPI therapy.
>
> Discontinue [PPI] and evaluate patients with an unexplained decrease in glomerular filtration rate for TIN. Discontinue PPIs in patients with prior history of PPI-induced TIN.[101]

Takeda was willing to accept the revision as drafted by FDA.[102] AstraZeneca, however, expressed its disagreement with certain aspects of the language proposed by the FDA and proposed alternative language.[103]

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[100] *See* AstraZeneca *Rieder* Preemption Mem. 27; FDA Safety Labeling Change Notification from Joyce A. Korvick, M.D., M.P.H., Deputy Dir. For Safety, to Emery Gigger, Regulatory Affairs Dir. (June 18, 2020), copy attached as Hindy Cert. I, Ex. TT, ECF No. 73-52.

[101] *See* AstraZeneca *Rieder* Preemption Mem. 27; FDA Safety Labeling Change Notification from Joyce A. Korvick, M.D., M.P.H., Deputy Dir. For Safety, to Emery Gigger, Regulatory Affairs Dir. (June 18, 2020), copy attached as Hindy Cert. I, Ex. TT, ECF No. 73-52; *see also* PSC Supp. FOF-COL ¶ 83.

[102] *See* Takeda Supp. FOF-COL ¶ 67.

[103] AstraZeneca Supp. FOF-COL ¶ 61 (citing AstraZeneca response to FDA safety labeling change notification (Oct. 14, 2020), copy attached as PSC Opp. Ex. 90).

By letter dated November 27, 2020, FDA approved the following Warnings and Precautions language addition to Nexium labeling ("November 2020 Warning"):

> Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue NEXIUM with suspected acute TIN.[104]

Notably, the warning ultimately approved by FDA accepted AstraZeneca's proposal to insert "acute" before "tubulointerstitial nephritis" and eliminated reference to "an asymptomatic gradual reduction in glomerular filtration rate" and "reported case series indicating that TIN was diagnosed on biopsy and in the absence of extra-renal manifestations of systemic inflammatory symptoms up to two years after the start of PPI therapy."

Although Takeda had indicated its willingness to accept FDA's original proposed language, because FDA accepted AstraZeneca's proposed changes to the proposed PPI class label amendment, FDA directed Takeda to modify its Prevacid label to include the PPI drug class warning reflecting AstraZeneca's changes:

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[104] AstraZeneca Supp. FOF-COL ¶ 62; FDA Supp. Approval from Joyce A. Korvick, M.D., M.P.H, Deputy Dir. Of Safety, to Emery Gigger, Regulatory Affairs (Nov. 27, 2020) at 10, Hindy Cert. I, Ex. VV, ECF No. 73-54.

> Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue PREVACID with suspected acute TIN.[105]

V. GOVERNING LEGAL STANDARDS

A. Preemption

The Supremacy Clause of the United States Constitution provides:

> This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.[106]

Under the Supremacy Clause, "[w]here state and federal law 'directly conflict,' state law must give way."[107] The "directly conflict" standard is a demanding one, rooted in the Tenth Amendment's preservation of the States' historic police powers unless superseded by a lawful act of Congress.[108]

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[105] *See* Takeda *Bales* Undisp. Facts ¶¶ 59-60; *see also* Email dated Nov. 9, 2020 from J. Lee, FDA to K. Shah, Takeda with final Warning language, copy attached as Anderson Cert. Ex. EE, No. 2:17-cv-06124, ECF No. 71-38.

[106] U.S. Const., Art. VI, cl. 2.

[107] *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 617 (2011).

[108] *Merck v. Albrecht*, 139 S. Ct. at 1677 (citing *Wyeth v. Levine*, 555 U.S. at 565).

Merck v. Albrecht and *Wyeth v. Levine* are the leading Supreme Court cases addressing the issue of whether and, if so, when FDA's actions under the FDCA preempt state laws requiring a warning beyond that contained in the FDA-approved prescription drug label. In those cases, the Supreme Court recognized that, in enacting the FDCA, Congress did not seek to occupy the field and expressly preempt all state laws addressing pharmaceutical safety, including through product liability lawsuits. To the contrary: as the Supreme Court recognized, Congress expressed "reluctance to displace state laws that would penalize drug manufacturers for failing to warn consumers of the risks associated with their drugs."[109] Indeed, Congress specifically *rejected* an express preemption provision with respect to federal drug regulation.

> Congress took care to preserve state law. The 1962 amendments added a saving clause, indicating that a provision of state law would only be invalidated upon a "direct and positive conflict" with the FDCA. . . . Consistent with that provision, state common-law suits "continued unabated despite . . . FDA regulation." *Riegel v. Medtronic, Inc.* (2008) (Ginsburg, J., dissenting); see *ibid.*, n 11 (collecting state cases). And when Congress enacted an express pre-emption provision for medical devices in 1976, see § 2, 90 Stat. 574 (codified at 21 U.S.C. § 360k(a)), it declined to enact such a provision for prescription drugs.[110]

Thus, the Supreme Court has held that Congress contemplated a role for both federal and state governments in regulating drug safety:

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[109] *Merck v. Albrecht*, 139 S. Ct. at 1677.

[110] *Wyeth v. Levine*, 555 U.S. at 567; *see also Merck v. Albrecht*, 139 S. Ct. at 1677.

> [W]e concluded that Congress enacted the FDCA "to bolster consumer protection against harmful products;" that Congress provided no "*federal* remedy for consumers harmed by unsafe or ineffective drugs"; that Congress was "awar[e] of the prevalence of state tort litigation;" and that, whether Congress' general purpose was to protect consumers, to provide safety-related incentives to manufacturers, or both, language, history, and purpose all indicate that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.[111]

The Supreme Court went on to observe that "[i]f Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history."[112] Congress never has done so.

In light of the clear "language, history, and purpose" of the FDCA, and the absence of an express preemption provision, the Supreme Court has been willing to find implied preemption of state laws regarding drug safety only in very narrow circumstances.[113] In *Wyeth v. Levine*, the Supreme Court held, and reiterated subsequently in *Merck v. Albrecht*, that federal preemption of a state law failure to warn claim could only be established if "'it was impossible for [the manufacturer] to comply with both federal and state requirements.'"[114] The question is "whether

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[111] *Merck v. Albrecht*, 139 S. Ct. at 1677 (citing *Wyeth v. Levine*, 555 U.S. at 574-75 (emphasis added)).
[112] *Merck v. Albrecht*, 139 S. Ct. at 1677 (quoting *Wyeth v. Levine*, 555 U.S. at 574).
[113] *Merck v. Albrecht*, 139 S. Ct. at 1677 (citing *Wyeth v. Levine*, 555 U.S. at 574-75).
[114] *Merck v. Albrecht*, 139 S. Ct. at 1678 (quoting *Wyeth v. Levine*, 555 U.S. at 571).

the relevant federal and state laws 'irreconcilably conflic[t].'"[115] The manufacturer defendant asserting the preemption defense bears the burden of establishing its validity.[116]

As it reiterated in *Merck v. Albrecht*, in *Wyeth v. Levine* the Supreme Court "acknowledged that meeting the standard we set forth would be difficult, but, we said, '[i]mpossibility pre-emption is a demanding defense.'"[117] Indeed, even though the Supreme Court recognized in *Wyeth v. Levine* the legal principle that a state failure to warn claim in a pharmaceutical product liability case could be preempted, the Supreme Court held that the state law claim in that particular case was *not* preempted because the manufacturer in that case could have changed the labeling of its drug to add a stronger warning.[118]

The "demanding" nature of the "impossibility preemption" defense for a manufacturer is due to two factors. First, "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."[119]

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[115] *Merck v. Albrecht*, 139 S. Ct. at 1679 (citing *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)).
[116] *See Wyeth v. Levine*, 555 U.S. at 571; *Merck v. Albrecht*, 139 S. Ct. at 1678.
[117] *Merck v. Albrecht*, 139 S. Ct. at 1678 (quoting *Wyeth v. Levine*, 555 U.S. at 572).
[118] *See Wyeth v. Levine*, 555 U.S. at 558, 581.
[119] *Merck v. Albrecht*, 139 S. Ct. at 1677 (citing *Wyeth v. Levine*, 555 U.S. at 570-71); *see also Wyeth v. Levine*, 555 U.S. at 568 (noting that in connection with 2007 FDCA amendments Congress rejected a provision that would have required FDA to preapprove all changes to drug labels and "adopted a rule of construction to make it

Second, FDA's CBE regulation permits branded drug manufacturers unilaterally to change a label without prior FDA approval to "reflect newly acquired information" if the changes "add or strengthen a . . . warning" for which there is "evidence of a causal association."[120] Even though FDA reviews CBE changes and may ultimately reject them after publication, "in the interim, the CBE regulation permits changes, so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both."[121]

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clear that manufacturers remain responsible for updating their labels.").

[120] 21 U.S.C. § 314.70(c)(6)(iii)(A); *see also Wyeth v. Levine*, 555 U.S. at 573 ("The CBE regulation permitted Wyeth to unilaterally strengthen its warning, and the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change.").

[121] *Merck v. Albrecht*, 139 S. Ct. at 1679. In light of my experience in pharmaceutical regulation, I recognize that, in practice, manufacturers infrequently seek to exercise unilateral authority to change a drug label by CBE. Rather, because the standard for changing a label by CBE or a PAS amendment is the same, and to avoid any risk of needless expense and confusion in the event FDA were to reject a CBE label change after implementation, manufacturers typically seek FDA approval before making any label change. Indeed, as explained above, that is what happened in 2006, when AstraZeneca informed FDA that it intended to amend the Nexium label to add interstitial nephritis as an Adverse Event – but also informed FDA that the change would not be implemented prior to FDA approval. However, notwithstanding industry practice, the Supreme Court's preemption opinions make clear that the significance of FDA's CBE regulation is that as a matter of law, it permits a branded drug manufacturer unilaterally to amend a label where the regulation's prerequisites for amendment are satisfied. *See Merck v. Albrecht*, 139 S. Ct. at 1678; *PLIVA, Inc. v. Mensing*, 564 U.S. at 625 n.8 (stating that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it" (citing *Wyeth v. Levine*, and finding preemption where FDA's CBE regulation did not apply to generic drug manufacturers)); *Wyeth v. Levine*, 555 U.S.

While FDA's CBE regulation poses a substantial hurdle to a manufacturer seeking to invoke "impossibility" conflict preemption, federal courts have not found that hurdle insurmountable. Indeed, just a few months ago, within this circuit and this district, the court found on remand from the Supreme Court's decision in *Merck v. Albrecht* that a state law failure to warn claim was preempted.[122]

To establish such impossibility, a manufacturer must provide "clear evidence that the FDA would not have approved a change to [the] label."[123] "Clear evidence" is "evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning."[124] The determination whether "clear evidence" has been provided is a legal determination to be made by the court.[125]

B. Summary Judgment Standard On Preemption Motions

In seeking summary judgment under Fed. R. Civ. P. 56, moving parties AstraZeneca and Takeda each bear the burden of stating the basis for their motion and "identifying those portions of the record that demonstrate the absence of a

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at 571-73.

[122] *See Fosamax.*, 2022 U.S. Dist. LEXIS 52627, at *35, *143-45.

[123] *Wyeth v. Levine*, 555 U.S. at 571; *see also Merck v. Albrecht*, 139 S. Ct. at 1678.

[124] *Merck v. Albrecht*, 139 S. Ct. at 1672.

[125] *Id.* at 1672, 1679.

genuine issue of material fact."[126] If the moving party meets its burden, the party opposing summary judgment "must set forth specific facts showing that there is a genuine issue for trial" and "may not rest upon the mere allegations or denials" of the pleading.[127] The evidence of the nonmovant is to be trusted and all inferences shall be drawn in his favor.[128] Moreover, the nonmovant "must identify specific facts and affirmative evidence that contradict those offered by the moving party."[129]

These familiar summary judgment standards must be applied taking into account the Supreme Court's holding in *Merck v. Albrecht* that "the question of pre-emption is one for a judge to decide, not a jury."[130] The Supreme Court explained that it reached this holding because

> The question often involves the use of legal skills to determine whether agency disapproval fits facts that are not in dispute. Moreover, judges, rather than lay juries, are better equipped to evaluate the nature and scope of an agency's determination.[131]

Even while characterizing preemption as predominantly a legal question, the Court also recognized that "sometimes contested brute facts will prove relevant to a

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[126] *Alley v. MTD Prods. Inc.*, 2017 U.S. Dist. LEXIS 208742 (W.D. Pa. Dec. 20, 2017).
[127] *Saldana v. Kmart Corp.*, 260 F.3d 228, 232 (3d Cir. 2001).
[128] *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 249 (1986) (quoting *Adickes v. S.H. Kress & Co.*, 398 U.S. 144 (1970)).
[129] *Solomon v. Bristol-Myers Squibb Co.*, 916 F. Supp. 2d 556 (D.N.J. 2013) (quoting *Anderson v. Liberty Lobby, Inc.*, 477 U.S. at 256-57).
[130] *Merck v. Albrecht*, 139 S. Ct. at 1672; *see also Merck v. Albrecht*, 139 S. Ct. at 1676.
[131] *Id.* at 1679-80.

court's legal determination about the meaning and effect of an agency decision."[132] In particular, it recognized that "in litigation between a drug consumer and a drug manufacturer (which will ordinarily lack an official administrative record for an FDA decision), the litigants may dispute whether the drug manufacturer submitted all material information to the FDA."[133] Nevertheless, the Court "consider[ed] these factual questions to be subsumed within an already tightly circumscribed legal analysis" and that the court, rather than a jury, was better positioned to "'resolve subsidiary factual disputes' that are part and parcel of the broader legal question."[134]

Thus, the Supreme Court's decision in *Merck v. Albrecht* modifies the normal summary judgment standard with respect to preemption motions. In deciding such motions the court, rather than the jury, is authorized to resolve "subsidiary factual disputes" to the extent necessary in connection with resolving the "broader legal question" of whether it would have been impossible for the manufacture to modify label warnings because there is clear evidence that FDA, after being fully informed of "all material information," would have rejected the change.[135] Accordingly, this R&R applies the *Merck v. Albrecht* principle in addressing the motions.

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[132] *Id.* at 1680.
[133] *Id.*
[134] *Id.*, quoting *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 327, (2015).
[135] *See Merck v. Albrecht*, 139 S. Ct. at 1680.

VI. ANALYSIS

A. The Relevance Of Timing To Preemption Analysis

There is no dispute that Defendants could have unilaterally amended their labels by the CBE process to add a warning if (1) "newly acquired information" established "reasonable evidence of a causal association" between a reported kidney injury adverse event and PPI use and (2) FDA, after having been fully informed of the justification for the warning, would not have prohibited or invalidated such a label change.[136]

B. Defendants' Argument That There Is No Preemption Because No "Newly Acquired Evidence" Regarding "Chronic Kidney Disease" Existed At The Time When Plaintiffs Consumed PPIs And Developed Chronic Kidney Disease

Defendants mount a threshold challenge to the assertion of failure to warn claims by Plaintiffs. Defendants' position is that during the period when Plaintiffs took PPIs and prior to their diagnoses of chronic kidney disease ("CKD"), there was

[136] *See supra* § V.A. I note that the hypothetical "would not have prohibited" standard articulated in *Wyeth v. Levine* remains the standard after *Merck v. Albrecht*. That is, to assert a preemption defense, a manufacturer is not required actually to have sought a label change and had the FDA reject it. *See In re Avandia Marketing, Sales and Prod. Liab. Litig.*, 945 F.3d 749, 759 (3d Cir. 2019); *see also Fosamax*, 2022 U.S. Dist. LEXIS 52627, at *67-68 (collecting cases and finding that "the 'universal' standard that a manufacturer need not submit a PAS and CBE to the FDA to preserve its preemption defense remains intact after [*Merck v. Albrecht*]."), *84-85 (manufacturer has no obligation to pursue a CBE amendment to preserve a preemption defense).

no scientific evidence that would have supported a warning regarding CKD. There are several elements to Defendants' argument:

First, Defendants assert that both Plaintiff Rieder and Plaintiff Bales (and others) were diagnosed with CKD (but not AIN) and allege that their consumption of PPIs was a cause of the CKD injury.[137]

Second, Defendants note that Plaintiffs Rieder and Bales started using PPIs in 2002 and 2005 respectively, and that both Mr. Rieder and Mr. Bales ceased using PPIs and were diagnosed with CKD prior to 2016; they make similar arguments with respect to other Plaintiffs.[138]

Third, Defendants quote a statement by Plaintiffs' expert Dr. Ross in his report that "[i]n 2016, Lazarus *et al*, was the first group of scientists to report on the association between PPI and CKD."[139]

Fourth, Defendants note that in 2020 FDA, after its TSI considering Lazarus and other studies, decided not to require a CKD warning.[140]

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[137] *See* AstraZeneca *Rieder* Preemption Mem. 4, 8; Takeda *Bales* Preemption Mem. 1-4. (The AstraZeneca *Rieder* Preemption Mem. addresses the points discussed in this paragraph with respect to both Plaintiffs Rieder and Bales.)

[138] AstraZeneca *Rieder* Preemption Mem. 4, 8; Takeda *Bales* Preemption Mem. 1-4.

[139] *See* AstraZeneca *Rieder* Preemption Mem. 22 (citing Expert Report of Dr. David Ross ¶ 317, No. 2:17-cv-06124, ECF Doc. 75-3 ("Ross Expert Report")); Takeda *Bales* Preemption Mem. 1-2 (citing Takeda *Bales* Undisp. Facts ¶ 31).

[140] *See* AstraZeneca *Rieder* Preemption Mem. 21-29; Takeda *Bales* Preemption Mem. 9-16.

Based on this chronology, Defendants argue that there was no information that could have constituted "newly acquired evidence" to support a label change to warn of "CKD" during Plaintiffs' use of PPIs or prior to their diagnoses of CKD. This argument fails for two related reasons. First, the argument confuses Plaintiffs' allegations of their ultimate injury from ingestion of PPIs with their claims of failure to warn. Plaintiff Rieder, Plaintiff Bales, and the Plaintiffs in the other four Bellwether Trial Cases allege an injury of CKD, but their failure to warn claims are broader than simply a failure to warn of CKD. Rather, as explained in Section II above, Plaintiffs' failure to warn claims are alleged in more general terms. They allege that "Defendants had a duty to warn Plaintiffs and their healthcare providers regarding the risks associated with ingesting PPI Products and failed to warn of the risk of kidney injuries that may be irreversible, permanently disabling and life-threatening."[141] And the complaints allege that PPIs can cause a variety of severe kidney injuries, including AIN, AKI, CKD and ESRD. The complaints further allege that the manufacturers provided inadequate warnings regarding the risk of kidney injuries.[142]

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[141] *See* Master Complaint ¶¶ 325, 327, 343; s*ee also supra* § II; PSC. Stmt. Of Undisp. Facts ¶¶ 7, 50 (Complaint alleges that labels should have contained warnings of a risk of "permanent or chronic renal injury" or potential "permanent and irreversible renal injuries."); *Lee* Compl. Count II; *Nelson* Compl. Count II.

[142] *See* Master Complaint Count III; *Lee* Compl. Count II; *Nelson* Compl. Count II. *See also* Master Complaint ¶¶ 179-211, 226 ("Consumers, including Plaintiffs, who have used Defendants' PPI Products have suffered from severe kidney injuries

Thus, with respect to kidney injuries, Plaintiffs have not asserted that the labels needed to warn specifically of "CKD". Rather, they allege that the labels should have contained warnings of a risk of "permanent or chronic renal injury" or potential "permanent and irreversible renal injuries."[143] Plaintiffs contend that, had such warnings been provided, their physicians would have been on notice of the risk and either chosen not to prescribe the PPI or arranged careful monitoring to detect any renal injury before it became irreversible and progressed to CKD.[144] It is undisputed that, during the time Plaintiffs used the PPIs at issue, the drug labels did not contain such warnings.[145] Plaintiffs also note, correctly, that a plaintiff asserting a failure to warn claim is not required to propose specific wording that should have been included in the label; rather, it is sufficient to describe the deficiencies in the existing warning in the labeling.[146]

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including, but not limited to, AIN, AKI, CKD and ESRD.").

[143] PSC. Stmt. Of Undisp. Facts ¶¶ 7, 50; *see also* Oral Args. 40:6-12, Apr. 5, 2022 (Mr. Autry: "There were no warnings in Takeda's label at the time about any possible harm to Bales' kidneys, zero, at the time that Bales took Prevacid. Dr. Fowler said that if he had known about the risk of kidney injuries, he would not have recommended PPIs to Mr. Bales."); Oral Args. 42:8-43:13, Apr. 5, 2022.

[144] *See supra* § II.

[145] *See supra* § IV.

[146] *See* PSC's Brief Opposing Defendants' Motions For Summary Judgment on Failure-to-Warn Preemption 11 (citing *Wyeth v. Levine*, 555 U.S. at 565 ("We therefore need not decide whether a state rule proscribing intravenous administration would be pre-empted. The narrower question presented is whether federal law pre-empts Levine's claim that Phenergan's label did not contain an adequate warning about using the IV-push method of administration.")).

Takeda's contrary argument in its supplemental briefing that warnings about

Second, as explained more fully in my R&R regarding the *Daubert* motions, Defendants' argument takes Dr. Ross's statement regarding the Lazarus study completely out of context.[147] Dr. Ross's report contains a lengthy and detailed review of scientific publications, clinical trial data, and post-marketing adverse event data linking PPI use with both acute tubulointerstitial nephritis (AIN) and chronic tubulointerstitial nephritis (CTIN).[148] Based upon these data, Dr. Ross concluded that "[t]he connection between acute and chronic injury in the tubulointerstitium is grounded in the understanding that interstitial nephritis constitutes 'a final common pathway to all forms of end-stage renal disease.'"[149] He further concluded that the risk that PPI use could have an adverse effect on the kidneys was known to

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the risk of injuries from PPIs other than the CKD with which Plaintiffs have been diagnosed are "beyond the scope of this case and irrelevant to the preemption question" fails because it relies on purported authority that is plainly inapposite. *See* Takeda Supp. FOF-COL ¶ 24 (citing *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp.2d 147, 163 (E.D.N.Y. 2001); *Peterson v. Sealed Air Corp.*, No. 86 C 3498, 1991 WL 66370, at *7 (N.D. Ill. Apr. 23, 1991)). Those out-of-circuit district court cases both predate *Wyeth v. Levine* and *Merck v. Albrecht* and have nothing to do with preemption. Rather, they are cases applying Federal Rule of Evidence 702 as interpreted by the Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and stand only for the unrelated proposition that expert testimony in a product liability case regarding a potential harm that plaintiff does not claim to have suffered does not fit the facts of the case and is not admissible in evidence because it will not assist the jury in deciding the case.

[147] *See* Report and Recommendation of Special Master Ellen K. Reisman Regarding *Daubert* Motions 58-59, No. 2:17-md-2789, ECF No. 811; Ross Expert Report 94-98.

[148] Ross Expert Report 98-248.

[149] Ross Expert Report 270 (quoting Neilson, "Pathogenesis and Therapy of Interstitial Nephritis", Kidney International, Vol. 35 (1989) 1257).

AstraZeneca and Takeda by the late 1990s and that "the threshold of reasonable evidence of a causal association between PPI use and chronic, progressive renal toxicity was crossed by early 2003."[150] Failure to warn of this risk, in Dr. Ross's view, resulted in the lack of monitoring and treatment of PPI users so that renal injury caused by PPI use would go undetected until it had progressed to CKD.[151] In his expert report, Dr. Ross opines that, well before 2016 and during the periods of Plaintiffs' PPI use, Defendants were on notice of an association between AIN and PPI use and of an association between CTIN and PPI use, and that they should have warned physicians and the public of these associations because, among other things, these conditions can lead to CKD.[152]

Accordingly, it is necessary to consider that earlier information, including information regarding adverse events of AIN, CTIN, and other renal injuries, that was published after the initial FDA approvals of Nexium and Prevacid, to determine whether it constituted "newly acquired evidence" sufficient to support a CBE amendment providing the more general warnings of kidney injury that Plaintiffs allege should have been included on the labels.

[150] Ross Expert Report 271-72.
[151] Ross Expert Report 272-74.
[152] Ross Expert Report 12, 94-250.

C. Whether FDA's PPI Labeling Decisions Are "Clear Evidence" That It Would Have Rejected A Kidney Injury Risk Warning If Defendants Had Sought To Provide One

The undisputed facts clearly reflect that after FDA's approval of Prevacid in 1995 and Nexium in 2001, there was "newly acquired information" about evidence of a causal association between PPIs and kidney injury, including AIN and its sequelae. As noted above, "newly acquired information" includes

> data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.[153]

The various 2003-2005 studies discussed in Section IV.C, above, amply satisfy that definition. AstraZeneca's submission of a CBE in March 2006 to amend the Adverse Reactions section of the label in reliance on Geevasinga (2005) and other information, and the 2005 FDA Office of Safety and Epidemiology review discussed previously, further confirm that there was "newly acquired information."

AstraZeneca's submission of a CBE to amend the Adverse Reactions section of the Nexium label based on the "newly acquired information" necessarily reflects its conclusion that there was "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[154] Thus, the only

[153] 21 C.F.R. § 314.3(b); s*ee also Wyeth v. Levine*, 555 U.S. at 569.
[154] 21 C.F.R. § 201.57(c)(7).

question is whether the newly acquired evidence also satisfied the somewhat more rigorous "reasonable evidence of a causal association" standard for a change to the Warnings and Precautions section of the labels.[155]

A fair reading of the 2003-2005 studies suggests that this "newly acquired evidence" could satisfy the "reasonable evidence of a causal association" standard for amending the Warnings and Precautions sections of the Nexium and Prevacid labels. In particular, the 2004 Torpey case series of 296 patients found an association between AIN and PPIs omeprazole and lansoprazole in one-third of the cases, noted that many patients stabilized after withdrawal of PPI, and that many patients did not present with traditional symptoms of AIN.[156]

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[155] As discussed in Section III, *supra*, the Warnings and Precautions section of a label must describe "clinically significant adverse reactions, (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class . . .), limitations on use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification)." 21 C.F.R. § 201.57(c)(6)(i).

[156] *See* PSC Supp. FOF-COL ¶ 43, PSC Opp. Ex. 31 (N. Torpey, T. Barker, and C. Ross, "*Drug-Induced Tubulo-Interstitial Nephritis Secondary to Proton Pump Inhibitors: Experience from a Single UK Renal Unit*," Nephrology Dialysis Transplantation 19, no. 6 (June 1, 2004): 1441-46); AstraZeneca's Response To PSC FOF-COL App. A at 3 (noting FDA awareness of Torpey, which is cited in 2005 Postmarketing Safety Review, Hindy Cert. I, Ex. CC, at 2, ECF No. 73-34); Takeda Supp. FOF-COL ¶ 33 (noting reference to Torpey in 2005 Takeda Prevacid Annual Report submission to FDA).

Moreover, and significantly, the studies included "dechallenge-rechallenge" case reports.[157] A "dechallenge-rechallenge" report is one in which a patient using a drug who experiences adverse symptoms discontinues the drug, the symptoms resolve, and then the patient resumes using the drug and again suffers the adverse symptoms. As AstraZeneca's regulatory expert Dr. Marianne Mann has explained,

> Rechallenge is simply that the patient presented perhaps with the AIN improved when the drug was withdraw[n], but that kidney toxicity recurred when that drug was reintroduced, really making, if you will, a tighter association between the drug and the event.[158]

As Dr. Mann also explained, determination of a causal association sufficient to support adding a warning to the Warnings and Precautions section of a label can be supported by case reports involving dechallenge and rechallenge.[159] In the language of the applicable regulation, dechallenge-rechallenge reports can support a

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[157] *See* PSC Supp. FOF-COL ¶¶ 39-45.

[158] Mann Dep. 157:7-13, PSC Opp. Ex. 21; *see also* PSC Supp. FOF-COL ¶ 19.

[159] Mann Dep. 157:7-13, 35:19-36:11; *see also* PSC Supp. FOF-COL ¶ 19. AstraZeneca notes that Dr. Mann's discussion of the potential significance of a dechallenge-rechallenge case study came in discussion of the FDA's 2014 label amendment, and that she testified that she thought it was "reasonable" for AstraZeneca to list AIN as an "adverse event" until 2014 because that is what the "large majority" of manufacturers did. AstraZeneca Resp. to PSC Supp. FOF-COL 7 (citing Mann. Dep. 160:11-161:25, 162:14-16). But that is beside the point for the preemption analysis. Dr. Mann's opinion that AstraZeneca's pre-2014 practice was "reasonable" does not address the issue whether the available evidence was sufficient to support a label amendment adding a warning in the Precautions section if Defendants had sought to do so. And her logic is somewhat circular in that it *assumes* the practice of other manufacturers was appropriate – which is precisely what is at issue in this MDL litigation.

conclusion of "reasonable evidence of causal association" sufficient to support addition of a warning.[160]

Indeed, FDA's March 2005 Guidance for Industry on Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment stated that

> FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including . . . evidence of positive dechallenge or positive rechallenge.[161]

And, FDA's regulation requiring post-marketing pharmacovigilance and adverse event reporting by manufacturers specifically requires that individual case safety reports specifically address "(vii) [w]hether adverse drug experience abated after drug use stopped or dose reduced;" and "(viii) [w]hether adverse drug experience reappeared after reintroduction of drug."[162]

Beyond this "newly acquired evidence," the 2006 Geevasinga and Simpson articles provided additional "reasonable evidence of a causal association."[163] Thus, by no later than 2006 and arguably earlier, there was ample "newly acquired

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[160] *See supra* § III.

[161] *See* https://www.fda.gov/files/drugs/published/Good-Pharmacovigilance-Practices-and-Pharmacoepidemiologic-Assessment-March-2005.pdf (last visited July 31, 2022); *see also* Ross Expert Report 101.

[162] 21 C.F.R. §§ 314.80(f)(3)(vii), (viii).

[163] *See supra* § IV.D; PSC Supp. FOF-COL ¶¶ 53-54 (citing PSC Opp. Ex. 37, 357-360); Takeda Supp. FOF-COL ¶ 4 (stating that "FDA was informed of and addressed Geevasinga (2006) in conjunction with Simpson in 2014 and 2018.")).

evidence" to support a labeling change and certainly no "clear evidence" that FDA would have rejected one had it been proffered.[164]

The undisputed facts undermine the Defendants' position that FDA would have rejected a proposal to amend the Warnings and Precautions section of PPI labels to provide additional information about the risk of AIN and its potential sequelae if they had ever made such a proposal, which they did not. The actual labeling history shows that FDA approved AstraZeneca's CBE to amend the Adverse Events section and required Takeda to make a similar amendment.[165] It also shows that after reviewing the 2011 Citizen's Petition and materials cited therein, and having the information in the 2006 Geevasinga and Simpson articles, along with other information, FDA required – for the first time – a PPI class label warning of the risk of potential AIN, including a direction to "[d]iscontinue [PPI] if acute interstitial nephritis develops."[166] As discussed above, the 2014 class label amendment required the manufacturers of PPIs to include the following language in the Warnings and Precautions section of the labels:

> Acute interstitial nephritis has been observed in patients taking PPIs including [PPI]. Acute interstitial nephritis may occur at any time

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[164] *See* PSC Supp. FOF-COL ¶ 45 & Ex. 32 (Nimeshan Geevasinga et al., "*Acute Interstitial Nephritis Secondary to Esomeprazole*," The Medical Journal of Australia 182, no. 5 (2005): 235-36 (discussing renal failure and ESRD, which can be downstream consequences of AIN)).

[165] *See supra* § IV.C.

[166] *See supra* § IV.D; AstraZeneca *Rieder* Preemption Mem. 21 (citing AstraZeneca, *Nexium* Label (Dec. 19, 2014), Hindy Cert. I, Ex. II § 5.3, ECF No. 73-40).

> during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue [PPI] if acute interstitial nephritis develops.[167]

That warning provided some – albeit limited – notice to physicians of kidney injury risk associated with PPIs. The 2014 label reflects that AIN "may occur at any time during PPI therapy." And while it states that AIN "is generally attributed to an idiopathic hypersensitivity reaction," it does not say that is the only possible cause, and it directs discontinuation of the PPI if AIN occurs. Contrary to Defendants' suggestion, this label change is not "clear evidence" that the FDA would have rejected a label change with a more robust warning of the risk of kidney injury if the manufacturers had proposed one during the 2006 to 2014 time frame.

Defendants argue that the language of the 2014 amendment providing an AIN warning must be read narrowly, to establish the outer limit of what language the FDA would have permitted had the manufacturer sought to provide it, but that argument does not withstand scrutiny.[168] The 2011 Citizen's Petition that led to that amendment referred to literature published over the past several years and requested only that PPI labels be amended to reflect the risks of AIN:

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[167] AstraZeneca *Rieder* Preemption Mem. 21 (citing AstraZeneca, *Nexium* Label (Dec. 19, 2014), Hindy Cert. I, Ex. II § 5.3, ECF No. 73-40).
[168] *See* Oral Args. 10:5-11:20, Apr. 5, 2022.

> *Acute interstitial nephritis*: Information regarding the potential for drug-induced acute interstitial nephritis, seen in at least 60 case reports, should be included in the appropriate section.[169]

Thus, the only request before FDA related to AIN. In the context of the regulatory history here, FDA's decision to require a class-wide amendment to PPI labeling to include language regarding AIN in the Warnings and Precautions section is not "clear evidence" that FDA would have rejected stronger or additional warnings if Defendants had sought to provide them in response to the information and literature developed prior to 2011 and thereafter.[170]

FDA's 2020 Proposed PPI Class Labeling Revision would have broadened the existing Warnings and Precautions language to include "tubulointerstitial nephritis", including asymptomatic TIN, and to recommend evaluation of patients with an unexplained decrease in glomerular filtration rate for TIN. This proposal by FDA in 2020 to expand significantly the warning language does not support a conclusion that FDA would have rejected a more robust warning if Defendants had proposed one at some earlier point in time. To be sure, FDA proposed that label

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[169] Citizen's Petition 3; *see also* Citizen's Petition 15-16.

[170] Defendants' observation that both the Citizen's Petition and the Pharmacovigilance Analysis performed by FDA's Center for Drug Evaluation and Research ("CDER") noted that AIN had the potential for "severe sequelae" including permanent kidney injury, does not change this conclusion. *See* AstraZeneca Resp. to PSC Supp. FOF-COL 3-4 (citing Citizen Petition and CDER Report); *see also* 2014 CDER Review 2, 15. To the contrary, it suggests that FDA might have been receptive to a CBE seeking a stronger warning.

change in 2020 after even more data regarding renal adverse events in patients taking PPIs were available. The point is not that this 2020 proposal proves definitively that FDA would have permitted the language in the 2020 Proposed PPI Class Labeling Revision earlier, but rather that it is hardly "clear evidence" that FDA would have rejected any proposals from the manufacturers to include more detailed information about the risk of renal injury at an earlier point in time.

Nor is the final FDA-approved 2020 amendment "clear evidence" that FDA would have rejected a more robust warning had Defendants proposed one earlier. The final 2020 label included the disclosure that patients could have silent AIN that "may occur at any point during PPI therapy" and in some cases was only "diagnosed on biopsy" because of "the absence of extra-renal manifestations (e.g., fever, rash or arthralgia)."[171] The 2020 labeling change disclosed that kidney injury is an ongoing risk requiring monitoring because it might be asymptomatic. And, since it was well known that undiagnosed and treated AIN could lead to permanent kidney injury, the amended 2020 label in effect warned of such injury too.[172] Certainly, the language as revised after AstraZeneca's objection provided a lesser warning than FDA's

[171] *See supra* § IV.E.

[172] *See* PSC Supp. Br. On Preemption 4 nn. 10-11 (Noting literature that TIN constitutes a final common pathway to all forms of end-stage renal disease and that TIN can be acute or chronic and that reports indicate that "30-70% of patients with acute interstitial nephritis did not fully recover renal function"); *see also supra* § IV.D.

original proposed language. But it is nonetheless a heightened warning of the risk of kidney injury. And, FDA's willingness to amend its proposed language in response to a request from AstraZeneca hardly provides "clear evidence" that the FDA would have rejected any proposals by the manufacturers over the approximately two decades from approval of Nexium and Prevacid in 2001 and 1995 respectively until 2020 to bolster the warnings regarding renal injuries, which they clearly could have done based upon the scientific data as reflected in the medical literature during that time frame.

In short, there is sufficient evidence to defeat summary judgment on preemption grounds, including that (i) when a CBE was proposed by a PPI manufacturer (AstraZeneca) to add "interstitial nephritis" to the Adverse Reactions section of the label in 2006, FDA approved it, (ii) at multiple points in time, there was "newly acquired evidence" from the medical literature that could have been used by the PPI manufacturers to support a request for additional warnings, (iii) the PPI manufacturers never sought such additional warnings either through a CBE or other means, and (iv) the actions taken by FDA in 2014 and 2020 do not provide "clear evidence" that, had such labeling changes been proposed, FDA would have rejected them.

D. *Fosamax*

In CMO No. 75, the parties were ordered to provide supplemental briefing regarding the recent decision in *Fosamax* by a different court in this district on remand from the Supreme Court in *Merck v. Albrecht*.[173] Having reviewed carefully the district court's decision in *Fosamax*, and the parties' briefing, it is clear that the *Fosamax* case is distinguishable from these PPI cases.

In *Fosamax*, unlike here, the manufacturer repeatedly pressed FDA for stronger warnings, which were repeatedly rejected by FDA.[174] In contrast, the undisputed facts here reflect that neither AstraZeneca nor Takeda ever sought to add language in the Warnings and Precautions section of their PPI labels concerning the risk of kidney injury with PPI use, and when FDA proposed strengthening the language in 2020, AstraZeneca sought to soften the language proposed by FDA.[175] Moreover, in *Fosamax* – unlike here – FDA itself filed papers in the litigation asserting that it was "fully informed" in reaching its decision.[176] In short, *Fosamax*

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[173] CMO No. 75.

[174] *See Fosamax*, 2022 U.S. Dist. LEXIS 52627, at *46-52, *111-16.

[175] *See supra* §§ IV.C, D, E. In this regard, AstraZeneca's observation that courts have held that a manufacturer's label change request is not a predicate for preemption is true but, once again, beside the point. *See* AstraZeneca Response To PSC Supp. FOF-COL 9 (citing *Fosamax* and other authorities). The relevance of AstraZeneca's conduct is that it is helpful in providing context for understanding and interpreting what the FDA's labeling decision means and indicates about what it would have done. *See Fosamax, supra*. This is not "speculation" about the FDA's intent.

[176] *See Fosamax*, 2022 U.S. Dist. LEXIS 52627, at *78-79, n. 15.

is a case where (i) the manufacturer repeatedly requested and the FDA repeatedly denied stronger warnings in the labeling prior to October 2010 and (ii) there was clear evidence, including from the FDA itself through the Solicitor General, that the FDA had in fact determined "that a new warning 'should [not] be included in the labeling of the drug[.]'"[177]

VII. CONCLUSION

As Judge Tjoflat recently observed in another case rejecting a manufacturer's argument that "impossibility" preemption barred failure to warn claims: "Federal preemption is a bitter pill. We should administer it carefully."[178] For the reasons set forth herein, I recommend that the motions for partial summary judgment as to Plaintiffs' failure to warn claims on grounds of preemption by federal law be denied. A proposed order is attached.

Respectfully submitted,

Date: 8/1/2022

Ellen K. Reisman
Special Master

[177] *Merck v. Albrecht,* 139 S. Ct. at 1686 (Alito, J., concurring) (citing Brief for the United States as *Amicus Curiae* 30, 33-34).
[178] *Carson v. Monsanto Company,* C.A. No. 21-10994 (11th Cir., July 12, 2022), slip op 1.