APPENDIX

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APPENDIX A

PRECEDENTIAL

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 22-3412

In re: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION

Phyllis Molnar and all other plaintiffs listed in Exhibit A to notice of appeal,

Appellants

On Appeal from the United States District Court
For the District of New Jersey
(D.C. No. 3-08-cv-00008)
District Judge: Honorable Freda L. Wolfson (Ret.)

Argued
March 5, 2024

Before: JORDAN, PHIPPS, and FREEMAN, *Circuit Judges*

(Filed: September 20, 2024)

David C. Frederick [ARGUED]
Ariela Migdal
James Ruck
Kellogg Hansen Todd Figel & Frederick
1615 M Street NW
Sumner Square, Suite 400
Washington, DC 20036

Mark Sparks
Ferguson Law Firm
3155 Executive Boulevard
Beaumont, TX 77705
Counsel for Appellants

John R. Boule III
Jeffrey R. Johnson
Jacob M. Roth [ARGUED]
Jones Day
51 Louisiana Avenue NW
Washington, DC 20001

Karen A. Confoy
Fox Rothschild
997 Lenox Drive
Princeton Pike Corporate Center, Building 3
Lawrenceville, NJ 08648

Stephen E. Marshall
Venable
750 E Pratt Street – Suite 900
Baltimore, MD 21202

Eileen O. Muskett
Fox Rothschild
1301 Atlantic Avenue
Suite 400, Midtown Building
Atlantic City, NJ 08401

Counsel for Appellee Merck Sharp & Dohme Corp

William B. Schultz
Zuckerman Spaeder
1800 M Street NW – Suite 1000
Washington, DC 20036

Counsel for Amicus Appellants Medshadow Foundation, Joshua M. Sharfstein, MD, Mary K. Pendergast, JD, and Jeremy Sharp

Robert S. Peck
Center for Constitutional Litigation
1901 Connecticut Avenue NW – Suite 1101
Washington, DC 20009

Counsel for Amicus Appellant Gregory Curfman, MD

Andrew N. Ferguson
Kevin M. Gallagher
Office of Attorney General of Virginia
202 N 9th Street
Richmond, VA 23219

Counsel for Amicus Appellants Commonwealth of Virginia, State of Alaska, State of Colorado, State of Connecticut, State of Delaware, State of Georgia, State of Illinois, State of Indiana, Commonwealth of Kentucky, State of Maryland, Commonwealth of Massachusetts, State of Minnesota, State of Mississippi, State of Montana, State of Nebraska, State of New Jersey, State of New Mexico, Commonwealth of Pennsylvania, State of South Carolina, State of Texas, State of Utah, and State of Vermont

Karen B. Menzies
KBM Law

6701 Center Drive W – Suite 1400
Los Angeles, CA 90045
Counsel for Amicus Appellants Joseph Lane, M.D., Vincent Vigorita, M.D., and David Burr, Ph.D.

Elizabeth J. Cabraser
Lieff Cabraser Heimann & Bernstein
275 Battery Street – 29th Floor
San Francisco, CA 94619

Avery S. Halfon
Lieff Cabraser Heimann & Bernstein
250 Hudson Street – 8th Floor
New York, NY 10013

Andrew R. Kaufman
Lieff Cabraser Heimann & Bernstein
222 Second Avenue South
Nashville, TN 37219

Ernest A. Young
3208 Fox Terrace Drive
Apex, NC 27502
Counsel for Amicus Appellant Public Law Scholars

OPINION OF THE COURT

JORDAN, *Circuit Judge*.

Drug manufacturers have the primary responsibility to ensure that the labels on their products comply with federal and state law. In this case, hundreds of Plaintiffs accuse drug manufacturer Merck Sharp & Dohme ("Merck" or the "Company") of failing to comply with drug labeling requirements under state law. According to the Plaintiffs, they were injured by the drug Fosamax and would not have taken it had they been properly warned. The District Court concluded at the summary judgment stage that the Plaintiffs' state law claims are preempted because Merck in fact proposed a label change that would have addressed the risk with Fosamax that the Plaintiffs complain of, but the Food and Drug Administration (the "FDA" or the "Agency") rejected the proposed change as lacking sufficient scientific support.

With real respect for the thorough and thoughtful work the District Court did in this complex case, we nonetheless conclude that it erred in its pre-emption analysis by giving too little weight to the required presumption against pre-emption. Applying that presumption, and considering the record here, we conclude that Plaintiffs' state law claims are not preempted. Accordingly, we will vacate the District Court's judgment for Merck and remand for further proceedings.

I. BACKGROUND

A. Statutory and Regulatory Background

1. Federal and State Power in Prescription Drug Labeling

"Throughout our [nation's] history the several States have exercised their police powers to protect the health and safety of their citizens" and "traditionally have had great latitude ... to legislate as to" those matters. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 475 (1996). "In the 1930's, Congress became increasingly concerned about unsafe drugs and fraudulent marketing, and it enacted the Federal Food, Drug, and Cosmetic Act (FDCA)." *Wyeth v. Levine*, 555 U.S. 555, 566 (2009) (citation omitted). Through the FDCA, Congress "charged the Food and Drug Administration with ensuring that prescription drugs are 'safe for use under the conditions prescribed, recommended, or suggested' in the drug's 'labeling.'" *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 302 (2019) (quoting 21 U.S.C. § 355(d)).[1] Accordingly, the FDA "regulates the safety information that appears on the labels of prescription drugs that are marketed in the United States."[2] *Id.* at 303.

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[1] Unless otherwise noted, all section references in this opinion are to the FDCA, ch. 675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301, *et seq.*), and its corresponding regulations (codified at 21 C.F.R. §§ 1.1, *et seq.*).

[2] The Supreme Court noted:

> Although we commonly understand a drug's "label" to refer to the sticker affixed to a prescription bottle, in this context the term refers more broadly to the written material that is sent to the physician who prescribes the drug and the written material that comes with the prescription bottle

"The FDCA's most substantial innovation was its provision for premarket approval of new drugs[, which] required every manufacturer to submit a new drug application ... to the FDA for review." *Wyeth,* 555 U.S. at 566. The statute originally prohibited a manufacturer from distributing a drug only if the FDA "determined that the drug was not safe for use as labeled[.]"[3] *Id.* But, "[i]n 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer" by requiring "the manufacturer to demonstrate that its drug was safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling before it could distribute the drug." *Id.* at 567 (internal quotation marks omitted).

Over time, as Congress "enlarged the FDA's powers to protect the public health and assure the safety, effectiveness, and reliability of drugs," it also "took care to preserve state law." *Id.* (internal quotation marks and citation omitted). "The 1962 amendments [to the FDCA] added a saving clause, indicating that a provision of state law would only be invalidated upon a direct and positive conflict with the FDCA." *Id.* (internal quotation marks omitted). "Consistent with that provision, state common-law suits continued unabated despite FDA regulation." *Id.* (cleaned up) (internal quotation marks omitted). Furthermore,

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> when the drug is handed to the patient at the pharmacy. These (often lengthy) package inserts contain detailed information about the drug's medical uses and health risks.

Merck Sharp & Dohme Corp. v. Albrecht, 587 U.S. 299, 303-04 (2019) (citation omitted).

[3] The manufacturer was permitted to distribute the drug if the FDA failed to respond within 60 days from the application's filing. *Wyeth v. Levine*, 555 U.S. 555, 566 (2009).

"when Congress enacted an express pre-emption provision for medical devices in 1976, it declined to enact such a provision for prescription drugs." *Id.* (citation omitted) (citing § 360k(a)).

2. Federal Drug Labeling Regulations

"FDA regulations set out requirements for the content, the format, and the order of the safety information on ... drug label[s]." *Albrecht*, 587 U.S. at 304 (citing § 201.57(c)). Labels must include various types of information, organized in a specific manner, by sections. § 201.57(a). Two sections of a label are relevant to this litigation: the "Warnings and Precautions" section, discussed in § 201.57(c)(6), and the "Adverse Reactions" section, covered by § 201.57(c)(7). The section "in which a particular risk appears on a drug label is an indicator of the likelihood and severity of the risk." *Albrecht*, 587 U.S. at 304. In the Warnings and Precautions section, a drug manufacturer "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[.]" § 201.57(c)(6)(i). That section "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[.]" *Id.* (emphasis added). "[A] causal relationship need not have been definitely established" before making such a revision. *Id.*

In the Adverse Reactions section of a label, the drug manufacturer must "describe the overall adverse reaction profile of the drug[,]" with "adverse reaction" being defined as "an undesirable effect, reasonably

associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." § 201.57(c)(7). "[That] definition does not include all adverse events observed during use of a drug, only those adverse events for which there is *some basis to believe there is a causal relationship* between the drug and the occurrence of the adverse event." *Id.* (emphasis added).

To summarize, risks described in the Warnings and Precautions section of a label (i.e., risks of clinically significant adverse reactions) are presumably more serious than those that appear only in the Adverse Reactions section. And, while the Warnings and Precautions section requires "reasonable evidence of a causal association with a drug" before a risk will be listed, § 201.57(c)(6)(i), drug manufacturers need only have "some basis to believe there is a causal relationship between [a] drug and the occurrence of [an] adverse event" to list the event in the Adverse Reactions section, § 201.57(c)(7). That "hierarchy of label information is designed to 'prevent overwarning' so that less important information does not 'overshadow' more important information[,]" *Albrecht*, 587 U.S. at 304 (quoting 73 Fed. Reg. 49603, 49605-06 (Aug. 22, 2008)), and the order represents an effort to avoid "'exaggeration of risk, or inclusion of speculative or hypothetical risks,' that 'could discourage appropriate use of a beneficial drug,'" *id.* (cleaned up) (quoting 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008)).

3. *Responsibilities of the Drug Manufacturer and the FDA in the Labeling Approval Process*

"Prospective drug manufacturers work with the FDA to develop an appropriate label when they apply for FDA approval of a new drug." *Id.* "[T]hrough many amendments to the FDCA and to FDA regulations" (*see supra* Section I.A.1.), "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Albrecht*, 587 U.S. at 312. Thus, "[a] drug manufacturer 'is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.'" *Id.* (quoting *Wyeth*, 555 U.S. at 571). "FDA regulations ... acknowledge that information about drug safety may change over time, and that new information may require changes to the drug label." *Id.* at 304 (citing §§ 314.80(c), 314.81(b)(2)(i)).

In 2007, Congress granted to the FDA, "[f]or the first time," the "authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval." *Wyeth*, 555 U.S. at 567 (citing § 901(a)). "In doing so, however, Congress did not enact a provision … that would have required the FDA to preapprove all changes to drug labels." *Id.* at 567-68 (citing S. 1082, 110th Cong. § 208 (2007) as passed). "Instead, it adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Id.* at 568; *see* § 355(o)(4)(I) ("This paragraph shall not be construed to affect the responsibility of the [drug manufacturer] ... to maintain its label in accordance with existing requirements[.]").

That does not mean, however, that manufacturers are free to make labeling changes without notifying the FDA. To change a drug's label, the manufacturer has to file a supplement to its new drug application. For "major changes," a manufacturer must submit a "Prior Approval Supplement," which requires FDA approval before the manufacturer can implement the proposed change. § 314.70(b). In contrast, for "moderate changes," the manufacturer files a "Changes Being Effected" ("CBE") supplement, which allows the manufacturer to make a labeling change without prior FDA approval. § 314.70(c). But the "FDA reviews all such submissions and may later deny approval of [a CBE] supplement[.]" 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). "Thus, in practice, manufacturers typically consult with [the] FDA prior to adding risk information to labeling." *Id.* A change to a drug's label may be considered a major change, § 314.70(b)(2)(v)(A), but a change in labeling "to reflect newly acquired information" in order to, among other things, "add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling" is, by regulation, classified as a moderate change, § 314.70(c)(6)(iii).

"During the course of reviewing an application[4] …, [the] FDA ... communicate[s] with applicants about

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[4] The FDCA regulations often refer to a "new drug application," but that term is defined to "includ[e] all amendments and supplements to the [initial] application." § 314.3(b); *see also* § 314.71(c) ("All procedures and actions that apply to applications under this part, including actions by applicants and the [FDA], also apply to supplements except as specified otherwise in this

scientific, medical, and procedural issues that arise during the review process." § 314.102(a). That "communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand." *Id.* The Agency is required to "make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in … application[s]" to "permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed." § 314.102(b).

If there are no reasons to deny the application, the FDA will send the applicant an approval letter. § 314.105(a). "[I]f the only deficiencies in the [application] concern editorial or similar minor deficiencies in the draft labeling," the "FDA will approve" the application, "conditioned upon the applicant incorporating the [FDA's] specified labeling changes." § 314.105(b).

On the other hand, if the FDA "determines that [it] will not approve" an application "in its present form," it will send the applicant something called a "complete response letter." § 314.110(a). Such a letter "describe[s] all of the specific deficiencies that the agency has identified in an application[,]" § 314.110(a)(1), and "reflects [the] FDA's complete review of the data submitted[,]" § 314.110(a)(2). Any "major scientific issues will ordinarily be addressed" in a complete response letter. § 314.102(b). Using a complete response letter, the Agency may deny an

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part."). Thus, regulations using the term "application" also apply to a drug manufacturer's labeling supplements.

application for many reasons, including if "[t]he proposed labeling is false or misleading in any particular." § 314.125(b)(6). If the FDA "determines ... that the data submitted are inadequate to support approval, the agency might issue a complete response letter without … reviewing proposed product labeling." § 314.110(a)(3).

"When possible, a complete response letter will recommend actions that the applicant might take to place the application … in condition for approval." § 314.110(a)(4). A complete response letter conveys "no implication as to the ultimate approvability of the application." 73 Fed. Reg. 39588, 39589 (July 10, 2008). After receiving such a letter, an applicant has several options. It may resubmit the application after "addressing all deficiencies identified in the complete response letter[,]" withdraw the application without prejudice, or request a hearing. § 314.110(b).

B. The Federal Pre-emption Doctrine in the Drug Labeling Context

Federal law is, of course, "the supreme Law of the Land." U.S. Const. art. VI, cl. 2. "[I]t has long been settled that state laws that conflict with federal law are without effect." *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 479-80 (2013) (internal quotation marks omitted). Here, Merck asserts that it has been put in an impossible dilemma because it cannot comply with both federal and state law labeling demands. The main question in the case thus concerns federal pre-emption of state law. As already mentioned, Merck makes the drug "Fosamax," which is prescribed to prevent and treat osteoporosis in post-menopausal women. *Albrecht*, 587 U.S. at 305. When evidence

emerged that Fosamax might actually cause bone fractures, especially of the femur, the need to warn doctors and patients, and the simultaneous need to comply with FDA regulations on label changes, created the cross-currents that have caught Merck in this long-running litigation.

There are "two cornerstones of ... pre-emption jurisprudence." *Wyeth*, 555 U.S. at 565. "First, the purpose of Congress is the ultimate touchstone in every pre-emption case." *Id.* (internal quotation marks omitted). "Second, in all pre-emption cases, and particularly in those in which Congress has legislated in a field which the States have traditionally occupied, we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Id.* (cleaned up). The Plaintiffs here claim that state law required Merck to add a warning about atypical femoral fractures to the Precautions section of the Fosamax label. At issue is whether federal law, specifically FDA regulations, prevented Merck from adding such a warning.

The Supreme Court's decision in *Wyeth v. Levine* sets forth the general federal pre-emption doctrine regarding brand-name drug labeling. 555 U.S. 555 (2009). In *Wyeth*, "the plaintiff developed gangrene after a physician's assistant injected her with Phenergan, an antinausea drug." *Albrecht*, 587 U.S. at 310. "The plaintiff brought a state-law failure-to-warn claim against Wyeth, the drug's manufacturer, for failing to provide an adequate warning about the risks that accompany various methods of administering the drug." *Id.* at 310-11. "A jury concluded that Wyeth's warning label was inadequate,

and that the label's inadequacy caused the plaintiff's injury." *Id.* at 311. "On appeal, Wyeth argued that the plaintiff's state-law failure-to-warn claims were pre-empted because it was impossible for Wyeth to comply with both state law duties and federal labeling obligations." *Id.* In short, as Merck does here, Wyeth advanced what is called an "impossibility pre-emption" defense. The question in *Wyeth* was "whether the FDA's approvals" regarding a drug's labeling provided a drug manufacturer "with a complete defense" to a plaintiff's tort claims under state law. *Wyeth*, 555 U.S. at 558-59.

After undertaking "a careful review of the history of federal regulation of drugs and drug labeling[,]" the Supreme Court "found nothing within that history to indicate that the FDA's power to approve or to disapprove labeling changes, by itself, pre-empts state law." *Albrecht*, 587 U.S. at 311. In fact, Congress, through the FDCA, "took care to preserve state law" and "did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Wyeth*, 555 U.S. at 567, 575. The Court was "unpersuaded by [the drug manufacturer]'s pre-emption argument[,]" given "Congress'[s] reluctance to displace state laws that would penalize drug manufacturers for failing to warn consumers of the risks associated with their drugs, and Congress'[s] insistence on requiring drug manufacturers to bear the responsibility for the content of their drug labels[.]" *Albrecht*, 587 U.S. at 312.

The Court "concluded, 'when the risk of gangrene from IV-push injection of Phenergan became apparent, Wyeth had a duty' under state law 'to provide a warning that adequately described that risk,

and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval.'" *Id.* (quoting *Wyeth*, 555 U.S. at 571). In sum, "[t]he CBE regulation permitted [the manufacturer] to unilaterally strengthen its warning, and the mere fact that the FDA approved Phenergan's label [did] not establish that it would have prohibited such a change." *Wyeth*, 555 U.S. at 573.

The Supreme Court declared that "[i]mpossibility pre-emption is a demanding defense." *Id.* In order to prove impossibility pre-emption in a failure-to-warn case, manufacturers must adduce "clear evidence that the FDA would not have approved a change to [the drug] label[.]" *Id.* at 571. Absent such evidence, the Court said, "we will not conclude that it was impossible for [the drug manufacturer] to comply with both federal and state requirements." *Id.*

C.Factual Background

"Fosamax belongs to a class of drugs called 'bisphosphonates.'"[5] *Albrecht*, 587 U.S. at 305. It and other bisphosphonates "work by affecting the bone remodeling process, that is, the process through which bones are continuously broken down and built back up again." *Id.* (internal quotation marks omitted). "For some postmenopausal women, the two parts of the bone remodeling process fall out of sync; the body removes old bone cells faster than it can replace them." *Id.* "That imbalance can lead to osteoporosis, a disease that is characterized by low bone mass and an increased risk of bone fractures." *Id.*

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[5] Fosamax's generic scientific name is "alendronate sodium." (J.A. at 1006).

"Fosamax (like other bisphosphonates) slows the breakdown of old bone cells and thereby helps postmenopausal women avoid osteoporotic fractures." *Id.* At the same time, however, "the mechanism through which Fosamax decreases the risk of osteoporotic fractures may increase the risk of" stress fractures. *Id.* While stress fractures "ordinarily heal on their own through the bone remodeling process[,]" "Fosamax and other bisphosphonates may cause stress fractures to progress to complete breaks that cause great pain and require surgical intervention to repair." *Id.* "When that rare type of complete, low-energy fracture affects the thigh bone, it is called an 'atypical femoral fracture.'" *Id.* at 306.

"[A]s far back as 1990 and 1991, when Fosamax was undergoing preapproval clinical trials, Merck scientists expressed concern in internal discussions that Fosamax could inhibit bone remodeling to such a profound degree that inadequate repair may take place and micro-fractures would not heal." *Id.* at 306 (internal quotation marks omitted). "When Merck applied to the FDA for approval of Fosamax, Merck brought those theoretical considerations to the FDA's attention." *Id.* "But, perhaps because the concerns were only theoretical, the FDA approved Fosamax's label [in 1995] without requiring any mention of this risk." *Id.*

Evidence that linked Fosamax to atypical femoral fractures continued to develop after 1995. *Id.* "Merck began receiving adverse event reports from the medical community indicating that long-term Fosamax users were suffering atypical femoral

fractures."[6] *Id.* "Merck performed a statistical analysis of [those] adverse event reports, concluding that [they] revealed a statistically significant incidence of femur fractures." *Id.* But "none of these studies concluded that Fosamax actually caused atypical femoral fractures, or even that they were definitively associated with Fosamax use." (J.A. at 45.)

In March 2008, Merck submitted a periodic safety update to the FDA that included thirty pages "dedicated to recent publications implicating a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures[.]" (J.A. at 45 (cleaned up).) That same month, Merck also sent the FDA a letter that was published in the New England Journal of Medicine "describing 'a potential link between [bisphosphonate] use and low-energy fractures of the femur.'" (J.A. at 46 (alteration in original).) Three months later, the FDA "requested information from all bisphosphonate drug manufacturers regarding this potential safety signal." (J.A. at 1160.) "Merck complied" by submitting the "additional data" it had received and the "investigations" it had conducted regarding femoral fractures. (J.A. at 46.)

While the FDA was analyzing that data, Merck submitted a Prior Approval Supplement asking "the FDA for preapproval to change Fosamax's label to add

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[6] One orthopedic surgeon called such fractures "Fosamax Fracture[s]" because "100% of patients in his practice who [had] experienced femoral fractures (without being hit by a taxicab)" had been taking Fosamax over an extended period of time. (J.A. at 959-60).

language to both the 'Adverse Reactions' and the 'Precautions'[7] sections of the label" regarding atypical femoral fractures. *Albrecht*, 587 U.S. at 307. In its submission, Merck explained that "[i]t is not possible with the present data to establish whether treatment with [Fosamax] increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures." (J.A. at 1257.) "Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, [Merck] believe[d] that it [was] important to include an appropriate statement about them in the product label." (J.A. at 1257.) In support of its application, "Merck submitted a lengthy analysis of femoral fractures in Fosamax users, cited to nine articles on such cases, and summarized the findings in a clinical overview." (J.A. at 47.) Merck proposed that the following language be added to the Precautions section of Fosamax's label:

> Low-Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced

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[7] Although the FDCA regulations call for a "Warnings and [P]recautions" section, § 201.57(c)(6), Merck's Fosamax label includes a section for Warnings and a separate section for Precautions. (*See* J.A. at 1278-79.) The proposed atypical femoral fractures risk was listed in the Precautions section, so, in keeping with the parties' practice, we sometimes use the term "Precautions" section instead of "Warnings and Precautions" section.

> prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

(J.A. at 1280 (cleaned up).) In addition to this warning in the Precautions section, Merck also "proposed adding a reference to 'low-energy femoral shaft fracture' in the Adverse Reactions section, and cross-referencing [the] discussion in the Precautions section." *Albrecht*, 587 U.S. at 307.

In April 2009, Merck employee Charlotte Merritt discussed the Company's pending Prior Approval Supplement with FDA officials Dr. Scott Monroe and Dr. Theresa Kehoe on a phone call. According to Merck's internal notes summarizing the call, Merritt explained to the FDA "that Merck was anxious to understand [the] FDA's timelines for completing their review of [the Fosamax Prior Approval Supplement and another labeling supplement] and that this information had not been forthcoming[.]" (J.A. at

1251.) Dr. Monroe explained that the FDA's "duration of review was related to [Merck's] elevation of [the atypical femoral fractures] issue to a [P]recaution in the labeling." (J.A. at 1251.) "He indicated that they could agree quickly to language in the [Adverse Reactions] section of the labeling[,]" but that the "FDA would like to approach the issue of a precaution from the [perspective][8] of all bisphosphonates" and was working to do so. (J.A. at 1251.) According to the call notes, "[t]he conflicting nature of the literature [did] not provide a clear path forward, ... [so] more time [was] need[ed] for [the] FDA to formulate a formal opinion on the issue of a [P]recaution around these data." (J.A. at 1251.) Dr. Monroe suggested that, "as an interim measure," Merck could amend only the Adverse Reactions section of the Fosamax label.[9] (J.A. at 1250.)

Because there was "some confusion regarding the [phone] discussion[,]" the FDA sent an email to Merck a week later stating that the Prior Approval Supplement "could be approved at this time only for inclusion of the atypical fracture language proposed in the ... adverse events section of the label." (J.A. at 1150.) The FDA told Merck that if it "agree[d] to hold off on the [Precautions section] language at [that]

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[8] The original uses the word "prospective." (J.A. at 1251.)

[9] Specifically, Merck's internal call notes provide that Dr. Monroe suggested Merck amend the "post-marketing section" of the Fosamax label. (J.A. at 1250.) That section is a subsection of the Adverse Reactions section. *See* § 201.57(c)(7)(ii)(B) (explaining that the "[p]ostmarketing experience" section "must list the adverse reactions ... that are identified from domestic and foreign ... reports); (*see also* J.A. at 1150 (the FDA calling the section the "postmarketing adverse events section of the label").)

time, then [it could] go ahead and close out these supplements." (J.A. at 1150.) The FDA said it "would then work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide on language" for the Precaution section, "if it is warranted." (J.A. at 1150.)

The next month, in May 2009, the FDA sent Merck a complete response letter (the "Complete Response Letter" or the "Letter"), authored by Dr. Monroe, that agreed to the addition of "low energy femoral shaft and subtrochanteric fractures" in the Adverse Reactions section but rejected Merck's proposed addition to the Precautions section. (J.A. at 1152-53.) The Agency's Letter explained the FDA's denial as follows:

> While the [FDA] agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

(J.A. at 1152-53.)

In the Complete Response Letter, the FDA told Merck that it had one year to "resubmit" its application, after "fully address[ing] all the deficiencies listed." (J.A. at 1153.) "Merck instead withdrew its application and decided to make the

changes [only] to the Adverse Reactions section through the CBE process." *Albrecht*, 587 U.S. at 307. It "made no changes to the Precautions section[.]" *Id.*

"[I]n March 2010, after reviewing the data submitted by Merck (and other manufacturers), the FDA issued a Drug Safety Announcement reiterating that there was not yet 'a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures.'" (J.A. at 49-50 (quoting J.A. at 1160).)[10] The FDA announced that it was "working closely with outside experts, including members of the recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force" (the "Task Force"), "to gather additional information that may provide more insight into [the] issue." (J.A. at 1160.)

Later that year, in September 2010, the Task Force published a report finding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture." (J.A. at 1078.) But that association "ha[d] not been proven to be causal." (J.A. at 1060.) The task force recommended that "[p]hysicians and patients should be made aware of the possibility of atypical femoral fractures … through a change in labeling of [bisphosphonates]." (J.A. at 1078.)

The next month, the FDA announced that it had determined that "atypical fractures may be related to long-term ... bisphosphonate use" and that it would require all bisphosphonate drug labels to include the

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[10] For convenience, throughout this opinion, we cite to the applicable pages in the joint appendix, which vary from the docket-item citations used by the District Court.

risk of atypical femoral fractures in the Warnings and Precautions section of the label. (J.A. at 1030.) The FDA held a conference call to discuss the announcement, in which the FDA's Deputy Director of the Office of New Drugs stated that the Task Force report "really helped [the FDA] understand these fractures a little bit better and ma[d]e [it] confident that this is something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for." (J.A. at 1139.)

On the same day as the FDA's announcement that it would require changes to bisphosphonate drug labeling, the Agency wrote to Merck requesting that the following language be added to the Precautions section of the Fosamax label:

Atypical Subtrochanteric and Diaphyseal Femoral Fractures:

> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
>
> Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to

> months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
>
> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

(J.A. at 1168-69 (cleaned up).)

In response, Merck "propos[ed] revised language that, once again, referred to the risk of 'stress fractures.'" *Albrecht*, 587 U.S. at 307. "But the FDA, once again, rejected that language" and sent Merck a redline rewriting Merck's proposal, deleting all references to stress fractures. *Id.* "[T]his time, the FDA explained that 'the term "stress fracture" was considered and was not accepted' because, 'for most practitioners, the term "stress fracture" represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use.'" *Id.* (quoting J.A. at 1192). "In January 2011, Merck added the FDA's language, nearly verbatim, to the Precautions section of the Fosamax label[,]" and "[t]hat warning remains in place today." (J.A. at 51-52.)

D. Procedural History

1. *Initial District Court Proceedings*

"The [Plaintiffs] here are more than 500 individuals who took Fosamax and who suffered atypical femoral fractures between 1999 and 2010." *Albrecht*, 587 U.S. at 308. "[I]nvoking federal diversity jurisdiction, [they] filed separate actions seeking tort damages on the ground that, during the relevant period, state law imposed upon Merck a legal duty to warn them and their doctors about the risk of atypical femoral fractures associated with using Fosamax." *Id.* "Merck argued, in response, that federal law preempted [the] Plaintiffs' claims – specifically, the May 2009 [Complete Response Letter] rejecting Merck's proposed label change." (J.A. at 53.)

"In 2011, the Judicial Panel on Multidistrict Litigation consolidated these cases ... for pre-trial administration in a multi-district litigation ('MDL') in the District of New Jersey" and assigned the case to the late Judge Joel A. Pisano. (J.A. at 53 n.6.) A bellwether trial was held in the so-called *Glynn* case. *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 951 F. Supp. 2d 695 (D.N.J. 2013), *vacated*, 852 F.3d 268 (3d Cir. 2017), *vacated and remanded sub nom. Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299 (2019) [hereinafter *Glynn*]. Prior to trial, Merck "moved for summary judgment based on federal preemption[.]" *Id.* at 700. The District Court "reserved decision on the federal preemption motion until there was a complete trial record in the case[.]" *Id.* At the conclusion of the trial, the jury returned a verdict for Merck, but the Court still decided to resolve the pre-emption question. *Id.* at 701.

The Court concluded that "preemption is warranted because … [t]he FDA's rejection constitutes clear evidence … that the FDA would not have approved a change to the Precautions section of the Fosamax label prior to Mrs. Glynn's injury[,]" which occurred in April 2009. *Id.* at 697, 703. The Court found that "the FDA never required [Merck] to submit new language or change the label, which demonstrates that the FDA did not think that the label should have been changed at that time."[11] *Id.* at 703-04.

"Merck then moved for an [order to show cause] why the claims of all other Plaintiffs with injury dates prior to September 14, 2010,[12] should not be dismissed pursuant to the Court's preemption ruling in *Glynn*[,]" which the Court granted. *In re Fosamax (Alendronate Sodium): Prods. Liab. Litig.*, MDL No. 2243, 2014 WL 1266994, at *2 (D.N.J. Mar. 26, 2014). The Court concluded that Merck was "entitled to judgment as a matter of law on all claims made by the Plaintiffs ... with injuries that occurred prior to September 14, 2010, because [the] Plaintiffs have failed to show cause

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[11] The Court further stated that the "Plaintiffs did not present any evidence at trial to refute preemption." *Glynn*, 951 F. Supp. 2d at 704. For example, they "did not offer any evidence that [Merck]'s [Prior Approval Supplement] was rejected due to language, specifically the use of 'stress fracture' instead of '[atypical femoral fracture],' or that the FDA would have approved a properly worded label change." *Id.* Nor did they "offer any evidence that [Merck] could have submitted a CBE supplement to change the Precautions section of the Fosamax label." *Id.* "[B]ased on [that] record[,]" the Court found that the "Plaintiffs' failure to warn claim [was] preempted." *Id.* at 705.

[12] September 14, 2010, is the date the Task Force published its report recommending a labeling change for Fosamax. *Glynn*, 951 F. Supp. 2d at 699.

why their claims are not preempted under [the] … ruling in *Glynn*." *Id.* at *17.

2. *Vacatur of the District Court's Glynn Decision*

In *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268, 302 (3d Cir. 2017), *vacated and remanded sub nom. Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299 (2019) [hereinafter *Fosamax I*], we vacated the District Court's decision and remanded for further proceedings. We explained that, in *Wyeth*, the Supreme Court "did not define the 'clear evidence' standard or explain how courts should apply it[,]" and noted that courts had applied the standard in different ways. *Id.* at 284. Interpreting the clear-evidence standard, we concluded:

> The term "clear evidence" ... does not refer directly to the *type* of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate. Rather, it specifies how *difficult* it will be for the manufacturer to convince the factfinder that the FDA would have rejected a proposed label change. The manufacturer must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by "clear evidence."

Id. at 285. Based on that conclusion, we reasoned that the Supreme Court "intended to announce a standard of proof when it used the term 'clear evidence' in *Wyeth*." *Id.* at 284. We held that, "to establish a preemption defense under *Wyeth*, the factfinder must conclude that it is highly probable that the FDA would not have approved a change to the drug's label." *Id.* at 286.

We then "conclude[d] that the question of whether the FDA would have rejected a proposed label change is a question of fact that must be answered by a jury." *Id.* We said that "[a]t root, *Wyeth* requires the decisionmaker to use an existing fact record to predict the outcome of a hypothetical scenario." *Id.* at 289. "The question posed to the decisionmaker in this case is: based on the contemporaneous medical literature and the interactions between Merck and the FDA that actually did happen, what would have happened if Merck had proposed the warning plaintiffs say was required?" *Id.* (emphasis omitted).

We determined that "a reasonable jury could conclude that Merck could have amended the Fosamax label via the CBE process" and that "a reasonable jury could also conclude that the FDA rejected Merck's proposed warning about femoral fractures in 2009 not because it denied the existence of a causal link between Fosamax and fractures, but because Merck repeatedly characterized the fractures at issue as 'stress fractures'" in the Prior Approval Supplement. *Id.* at 297-98. We thus vacated the District Court's grant of summary judgment to Merck and remanded for further proceedings. *Id.* at 302.

3. *The Supreme Court Vacates our Fosamax I Decision*

Merck filed a petition for a writ of certiorari, and, "[i]n light of differences and uncertainties among the courts of appeals and state supreme courts in respect to the application of *Wyeth*," the Supreme Court granted the writ. *Albrecht*, 587 U.S. at 310.

In *Merck Sharp & Dohme Corp. v. Albrecht*, the Court "elaborate[d] *Wyeth*'s requirements" and

created a two-pronged test that courts must use to determine whether the drug manufacturer showed by clear evidence that "federal law prohibited the drug manufacturer from adding a warning that would satisfy state law[.]" 587 U.S. at 310, 314. Clear evidence, it said, "is evidence that shows the court[, first,] that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and[, second,] 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." *Id.* at 303.

The Supreme Court declared that meeting that standard would be "difficult" because "impossibility pre-emption is a demanding defense." *Id.* at 313 (cleaned up). Indeed, it stated that "[t]he underlying question for this type of impossibility pre-emption defense is whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding *any and all* warnings to the drug label that would satisfy state law." *Id.* at 313-14 (emphasis added). And, as it had "cautioned many times before," the Court reminded litigants and lower courts that the "'possibility of impossibility [is] not enough.'" *Id.* at 314 (alteration in original) (quoting *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 625 n.8 (2011)). Of high significance here, the Court observed that because "federal law – the FDA's CBE regulation – permits drug manufacturers to change a label ... without prior approval from the FDA[,] … 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." *Id.* at 314-15.

Against that background, the Court assigned responsibility for assessing an impossibility defense to judges rather than juries. It chose not to "define *Wyeth*'s use of the words 'clear evidence' in terms of evidentiary standards, such as 'preponderance of the evidence' or 'clear and convincing evidence' and so forth, because ... courts should treat the critical question not as a matter of fact for a jury but as a matter of law for the judge to decide." *Id.* at 315. "And where that is so, the judge must simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflic[t].'" *Id.* (alteration in original) (quoting *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)).

The Court noted that "the only agency actions that can determine the answer to the pre-emption question, of course, are agency actions taken pursuant to the FDA's congressionally delegated authority[,]" and it listed some of the means by which that can be done, including the issuance of a complete response letter under § 314.110(a):

> Federal law permits the FDA to communicate its disapproval of a warning by means of notice-and-comment rulemaking setting forth labeling standards, *see, e.g.*, 21 U.S.C. § 355(d); 21 C.F.R. §§ 201.57, 314.105; by formally rejecting a warning label that would have been adequate under state law, *see, e.g.*, 21 C.F.R. §§ 314.110(a), 314.125(b)(6); or with other agency action carrying the force of law, *cf., e.g.*, 21 U.S.C. § 355(o)(4)(A).

Id. at 315-16. The Court disclaimed making any ruling about what agency action would carry the force

of law because "[t]he question of [a] disapproval 'method' [was] not [then] before [it]." *Id.* at 316. But it wanted to make "the obvious point that, whatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated."[13] *Id.*

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[13] Justice Thomas wrote separately in *Albrecht* to "explain [his] understanding of the relevant pre-emption principles and how they apply to this case." 587 U.S. at 318 (Thomas, J., concurring). Pertinent here, Justice Thomas explained that "Merck's impossibility pre-emption defense fails because it does not identify any federal law that prohibited it from adding any and all warnings that would satisfy state law[,]" – reasoning that, "[b]y its reference to 'the Laws of the United States,' the Supremacy Clause requires that pre-emptive effect be given only to those federal standards and policies that are set forth in, or necessarily follow from, the statutory text that was produced through the constitutionally required bicameral and presentment procedures." *Id.* at 321 (cleaned up). He asserted that the Complete Response Letter that denied Merck's proposed labeling changes "neither marked 'the consummation of the agency's decisionmaking process' nor determined Merck's 'rights or obligations[;]' [i]nstead, it was 'of a merely tentative or interlocutory nature'" because such letters "merely 'infor[m] sponsors of changes that must be made before an application can be approved, *with no implication as to the ultimate approvability of the application*.'" *Id.* at 322 (citation omitted) (first quoting *Bennett v. Spear*, 520 U.S. 154, 178 (1997) and then quoting 73 Fed. Reg. 39588, 39589 (July 10, 2008)). Therefore, he concluded that "the [L]etter was not a final agency action with the force of law, so it cannot be 'Law' with pre-emptive effect." *Id.*

Justice Thomas further reasoned that "Merck's argument that the 2009 [L]etter and other agency communications suggest that the FDA would have denied a future labeling change fares no better" because "hypothetical agency action is not 'Law.'" *Id.* He explained that "Merck's primary argument, based on various agency communications, is that the FDA would have rejected a hypothetical labeling change submitted via the CBE process." *Id.*

The Supreme Court then elaborated on the judge-or-jury issue, saying "the question of agency disapproval … is a legal one for the judge, not a jury" because "[t]he question often involves the use of legal skills to determine whether agency disapproval fits facts that are not in dispute." *Id.* "Moreover," the Court said, "judges, rather than lay juries, are better equipped to evaluate the nature and scope of an agency's determination" because they "are experienced in the construction of written instruments, such as those normally produced by a federal agency to memorialize its considered judgments." *Id.* (cleaned up). "And judges are better suited than are juries to understand and to interpret agency decisions in light of the governing statutory and regulatory context." *Id.* The Court also reasoned that, "[t]o understand the question as a legal question for judges makes sense given the fact that judges are normally familiar with principles of administrative law." *Id.* at 317. It predicted that viewing the question as a legal one "should produce greater uniformity among courts[,]" and it remarked that "greater uniformity is normally a virtue when a question requires a determination concerning the scope and effect of federal agency action." *Id.*

Accordingly, the Supreme Court vacated our judgment in *Fosamax I* and remanded the case to us for further proceedings "[b]ecause [we] treated the pre-emption question as one of fact, not law, and

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at 321. But, in his view, "neither agency musings nor hypothetical future rejections constitute pre-emptive 'Laws' under the Supremacy Clause." *Id.*

because [we] did not have an opportunity to consider fully the standards" it had set forth. *Id.* at 318.[14]

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[14] Justice Alito, with whom Chief Justice Roberts and Justice Kavanaugh joined, wrote a separate concurring opinion explaining that he only concurred in the judgment "because [he] agree[d] with the Court's decision on the only question that it actually decides, namely, that whether federal law allowed Merck to include in the Fosamax label the warning alleged to be required by state law is a question of law to be decided by the courts[.]" *Albrecht*, 587 U.S. at 323 (Alito, J., concurring). But he did not join the opinion "because [he was] concerned that its discussion of the law and the facts may be misleading on remand." *Id.*

Justice Alito noted "a statutory provision ... that may have an important bearing on the ultimate pre-emption analysis in this case." *Id.* at 324. Under § 355(o)(4)(A), "which was enacted in 2007, Congress has imposed on the FDA a duty to initiate a label change '[i]f the Secretary becomes aware of new information, including any new safety information … that the Secretary determines should be included in the labeling of the drug.'" *Id.* He explained:

> This provision does not relieve drug manufacturers of their own responsibility to maintain their drug labels, but the FDA's actions taken pursuant to this duty arguably affect the pre-emption analysis. This is so because, if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified. The FDA's duty does not depend on whether the relevant drug manufacturer, as opposed to some other entity or individual, brought the new information to the FDA's attention. Nor does § 355(o)(4)(A) require the FDA to communicate to the relevant drug manufacturer that a label change is unwarranted; instead, the FDA could simply consider the new information and decide not to act.
>
> Section 355(o)(4)(A) is ... highly relevant to the pre-emption analysis, which turns on whether federal law (*including*

4. *District Court Decision on Remand*

"Upon remand, [we] returned the case to [the District] Court to decide 'in the first instance whether the [P]laintiffs' state law claims are preempted by federal law under the standards described by the Supreme Court.'"[15] (J.A. at 38 (quoting Order at 1, *In Re: Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, No. 14-1900 (3d Cir. Nov. 25, 2019)).) We instructed the District Court "to determine the effect of the [FDA]'s Complete Response Letter ... and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." *Id.*

The District Court granted Merck's motion for summary judgment and issued a carefully reasoned 87-page opinion concluding that Merck "fully informed the FDA of the justifications for its proposed warning, ... and the FDA, in turn, informed [Merck] that it would not approve changing the Fosamax label to include that warning in the [Complete Response Letter]." (J.A. at 38-39.) After combing "through the extensive record," the Court found that, "[b]etween its formal safety updates, periodic emails, and [Prior

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appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law.

Id. at 324-25 (cleaned up). And Justice Alito "assume[d]" that on remand, "the Court of Appeals will consider the effect of § 355(o)(4)(A) on the pre-emption issue in this case." *Id.* at 325. He also critiqued the Supreme Court's recitation of the facts in this case, saying that the Court provided "a one-sided account" in favor of the Plaintiffs. *Id.* at 326.

[15] The MDL was reassigned to then-Chief Judge Freda L. Wolfson.

Approval Supplement], [Merck] clearly and fully informed the FDA of the panoply of risks associated with long-term Fosamax use and the justifications for its proposed label change." (J.A. at 70.) That satisfied the first prong of the *Albrecht* pre-emption test.

As to the second prong of that test – whether the FDA informed Merck that it would reject any warning about atypical femoral fractures in the Precautions section of Fosamax's label – the Court "appreciate[d] that, as worded, the language of the [Complete Response Letter] gives rise to competing inferences with respect to why the FDA rejected [Merck]'s warning." (J.A. at 96.) Given that ambiguity, the Court said, "[i]f the [Letter] were the sum total of the evidence of FDA action in this case, [the] Plaintiffs might be on firmer footing with regards to their preemption arguments." (J.A. at 97.) But it went on to say that "the [Complete Response Letter] does not tell the whole story without the proper context gleaned from other FDA communications." (J.A. at 99.) Although "informal communications do not constitute 'Laws' with the power to preempt[,]" the Court reasoned, it was still "appropriate to consider [those] communications for [the] limited purpose" of "shed[ding] light on the meaning and scope of the [Letter]." (J.A. at 98 (internal quotation marks omitted).) Upon considering the Complete Response Letter "in light [of] the FDA's communications," the Court concluded that the Letter "rejected [Merck]'s Precautions warning because the FDA doubted the evidence linking bisphosphonate use to atypical femoral fractures in a causal sense[,]" not because of Merck's use of the term "stress fractures." (J.A. at 103.)

The District Court also analyzed how the FDCA's regulatory regime fits into the pre-emption analysis. It considered § 355(o)(4)(A), which, as previously noted (*supra* note 14), requires the FDA to tell the drug manufacturer if the Agency "becomes aware of new information" that "should be included in the labeling of the drug[.]" 21 U.S.C. § 355(o)(4)(A). Because of that provision, the Court said, "it is improbable that the FDA declined to approve [Merck]'s Precautions warning, or failed to propose a solution to the problem it perceived with the language, *i.e.*, stress fracture, all while the FDA had sufficient causal evidence linking bisphosphonates to atypical femoral fractures and thus exposing patients to the risk of severe injury in the interim." (J.A. at 105-06.) The Court thought that "[t]he more likely scenario is that the FDA's actions taken in this case convey doubts that the Agency had about the underlying science, a deficiency no revision or edits could solve; hence, the Agency did not propose any." (J.A. at 106 (emphases omitted).)

The Court also disagreed with the Plaintiffs' argument that Merck could have amended the Precautions section of the Fosamax label through a CBE amendment after the FDA denied Merck's Prior Approval Supplement. It explained that "[t]he CBE process permits a drug manufacturer to unilaterally add a Precautions warning to its label, but only if 'newly acquired information' provides 'reasonable evidence of a causal association['] of a ['clinically significant adverse reaction['] linked to a drug." (J.A. at 112 (quoting §§ 314.70(c)(6)(iii), 201.57(c)(6)(i)).) After analyzing Agency announcements and the Task Force's report, the Court determined that "there was no 'newly acquired information' as defined in the CBE

regulation on the basis of which [Merck] could have successfully submitted a CBE amendment" after the FDA denied Merck's Prior Approval Supplement.[16] (J.A. at 117.)

For those reasons, the Court granted Merck's motion for summary judgment, concluding that the Plaintiffs' state law claims were preempted. The Plaintiffs have appealed.[17]

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[16] In determining whether newly acquired information had arisen during the period of time between the FDA's denial of Merck's Prior Approval Supplement and issuance of the Task Force report, the District Court may have been responding to the Supreme Court's statement from *Albrecht* that, because of the FDA's CBE regulation, "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." 587 U.S. at 315. Merck argues that the District Court's finding that no new information had arisen was correct because the "Plaintiffs did not provide or even summarize" any new information that arose during that period and "thereby waived any such argument[.]" (Answering Br. at 32 n.2.) That said, "Merck conceded that the FDA's CBE regulation would have permitted Merck to try to change the label to add a warning" prior to the FDA's denial of that supplement. *Albrecht*, 587 U.S. at 308-09.

[17] Virginia and twenty-two other states (Alaska, Colorado, Connecticut, Delaware, Georgia, Idaho, Illinois, Indiana, Kentucky, Maryland, Massachusetts, Minnesota, Mississippi, Montana, Nebraska, New Jersey, New Mexico, Pennsylvania, South Carolina, Texas, Utah, and Vermont) filed an amicus brief in favor of the Plaintiffs, as did "Public Law Scholars," a group of law professors whose scholarship has addressed federal pre-emption of state law. The following also filed amicus briefs: Dr. Gregory Curfman; Drs. Joseph Lane, Vincent Vigorita, and David Burr; and MedShadow Foundation and three former FDA officials.

II. DISCUSSION[18]

On appeal, the Plaintiffs argue that the District Court erred in concluding Merck satisfied the *Albrecht* pre-emption test. They contend that Merck failed on both prongs, that in reality "Merck failed to fully inform [the] FDA of the justifications for the warning, required by state law, that Fosamax can cause atypical femoral fractures" and that "Merck likewise cannot show that [the] FDA informed it that [the] FDA would disapprove a change to Fosamax's label to warn of atypical femoral fractures." (Opening Br. at 25.) The Plaintiffs also argue that the Complete Response Letter in this case did not carry the force of law and that FDA regulations allowed Merck to make appropriate labeling changes through the CBE process. Merck, in response, asserts that it met its burden on both prongs of the *Albrecht* pre-emption test, that the Complete Response Letter had the force of law, and that the CBE process adds nothing to the pre-emption analysis here.

Before discussing the parties' specific arguments about pre-emption, we first have to consider our standard of review.

A. Standard of Review.

The overall pre-emption question in this case is one of law. That much is clear after *Albrecht*.[19] 587 U.S.

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[18] The District Court had jurisdiction under 28 U.S.C. § 1332(a). We have jurisdiction pursuant to 28 U.S.C. § 1291.

[19] Few Courts of Appeals have had occasion to apply the *Albrecht* pre-emption test in the drug labeling context. *See, e.g.*, *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 57 F.4th 327 (1st Cir. 2023); *Knight v. Boehringer Ingelheim Pharms., Inc.*, 984 F.3d 329 (4th Cir. 2021); *Hickey v. Hospira, Inc.*, 102 F.4th 748 (5th

at 318 (vacating *Fosamax I* because we "treated the pre-emption question as one of fact, not law"). But the parties disagree on the level of deference we must give to the District Court's determinations that Merck satisfied both prongs of *Albrecht*'s pre-emption test. The Plaintiffs argue that we should review the entirety of "the District Court's preemption determination, including its construction of [the] FDA's Letter, de novo." (Reply Br. at 3 (cleaned up).) Merck argues that "the two prongs of the preemption test in this case hinge on factual determinations," and that the District Court's determinations for each prong should accordingly be reviewed for clear error. (Answering Br. at 21.)

The Supreme Court explained in *Albrecht* that the pre-emption question in reality "falls somewhere between a pristine legal standard and a simple historical fact[,]" notwithstanding its ultimate characterization as one of law. 587 U.S. at 317 (quoting *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996)). The Court acknowledged that "sometimes contested brute facts will prove relevant to a court's legal determination about the meaning and effect of an agency decision." *Id.* "For example," it said, "if the FDA rejected a drug manufacturer's supplemental application to change a drug label on the ground that the information supporting the application was insufficient to warrant a labeling change, the meaning and scope of that decision might

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Cir. 2024); *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882 (7th Cir. 2020). We could find no case that engages in a substantive discussion about the proper standard of review in the *Albrecht* pre-emption context, nor have the parties pointed us to any.

depend on what information the FDA had before it." *Id.* Moreover, "the litigants may dispute whether the drug manufacturer submitted all material information to the FDA." *Id.* The Court considered those "factual questions to be subsumed within an already tightly circumscribed legal analysis[,]" and it "[did] not believe that they warrant submission alone or together with the larger pre-emption question to a jury." *Id.*

"Generally, questions of law are reviewed de novo and questions of fact, for clear error[.]" *Monasky v. Taglieri*, 589 U.S. 68, 83 (2020). Thus, although we are bound to review the District Court's overall pre-emption conclusion de novo, *In re Avandia Mktg., Sales & Prods. Liab. Litig.*, 945 F.3d 749, 757 (3d Cir. 2019) (exercising plenary review when applying the *Albrecht* pre-emption standard), when a district court resolves "subsidiary factual matters ... in the course of" deciding that ultimate legal question, we will review those findings under a "clearly erroneous" standard. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 324 (2015). This seems the best approach not only on general principles but also because the justification given by the Supreme Court for its analytical approach in *Albrecht* is akin to the justification it gave when tasking judges with construing claim terms in a patent.

In its landmark decision in *Markman v. Westview Instruments, Inc.*, the Court described claim construction as a "mongrel practice," 517 U.S. at 378, just as it described the pre-emption analysis in *Albrecht* as posing neither a "pristine legal standard" nor a question of "simple historical fact," 587 U.S. at 317 (quoting *Markman*, 517 U.S. at 388). Despite the

factual questions that often arise in construing patent claims, the Court in *Markman* deemed it best to entrust the whole interpretative process to judges rather than juries. It said, "as a matter of the sound administration of justice, one judicial actor is better positioned than another to decide the issue in question" and that "judges, not juries, are ... better suited to find the acquired meaning of patent terms." *Markman*, 517 U.S. at 388. That has a distinctly similar ring to the language used in *Albrecht*, which in fact quotes *Markman*. *Albrecht*, 587 U.S. at 316, 318 (explaining that "judges, rather than lay juries, are better equipped to evaluate the nature and scope of an agency's determination" and, quoting *Markman*, holding that the "better positioned" decisionmaker in pre-emption cases is a judge).

When the Supreme Court later, in *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, looked closely at the question of how much deference an appellate court should give to a district court's fact-finding during claim construction, it ruled that the clearly erroneous standard should apply. 574 U.S. at 324. We do not think it a mere coincidence that in *Albrecht* the Supreme Court quoted *Teva* in declaring, "'courts may have to resolve subsidiary factual disputes' that are part and parcel of the broader legal question." *Albrecht*, 587 U.S. at 317 (quoting *Teva*, 574 U.S. at 327). Accordingly, the clear-error standard of review applies to any subsidiary factual determinations the District Court made in this case. *Teva*, 574 U.S. at 324. The importance of a district court's subsidiary fact finding may vary because, "[i]n some instances, a factual finding will play only a small role in a judge's ultimate legal conclusion[,] ... [b]ut in

some instances, a factual finding may be close to dispositive of the ultimate legal question[.]" *Id.* at 333.

With the foregoing principles in mind, we undertake a de novo review of the District Court's conclusion that the Plaintiff's state law claims were preempted by federal law, while giving clear-error deference to subsidiary factual findings.[20]

B. The Plaintiffs' State Law Claims are Not Preempted.

1. *Prong #1: The District Court Did Not Err in Concluding that Merck Fully Informed the FDA about the Risks of Atypical Femoral Fractures.*

The parties dispute whether Merck "fully informed the FDA of the justifications for the warning required by state law[.]" *Albrecht*, 587 U.S. at 314. Resolving

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[20] Normally, "[s]ummary judgment should be granted only if a court concludes that 'there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law.'" *Ideal Dairy Farms, Inc. v. John Labatt, Ltd.*, 90 F.3d 737, 743 (3d Cir. 1996) (emphasis omitted) (quoting Fed. R. Civ. P. 56). And "[a]n appellate court reviews the district court's grant of summary judgment de novo, applying the same standard as the district court[,]" which requires the court to "view the underlying facts and all reasonable inferences therefrom in the light most favorable to the party opposing the motion." *Id.* But that traditional standard is effectively modified in cases like this because the Supreme Court has instructed judges to resolve subsidiary fact questions rather than leave them for juries to decide. *See Albrecht*, 587 U.S. at 315, 317 (explaining that "courts should treat the [agency disapproval] question not as a matter of fact for a jury but as a matter of law for the judge to decide" and that any relevant "contested brute" fact questions are "subsumed within an already tightly circumscribed legal analysis" and do not "warrant submission alone or together with the larger pre-emption question to a jury").

that dispute requires a fact-intensive analysis, as is evident by the parties' disagreement about how the information provided to the FDA was portrayed. Indeed, the Supreme Court's examples of "contested brute facts" in *Albrecht* – "what information the FDA had before it" and "whether the drug manufacturer submitted all material information to the FDA" – are among the central issues in this case. *Id.* at 317.

The Plaintiffs contend that the District Court improperly "credited Merck's 2008 safety update," which "downplayed the risk of atypical femoral fractures." (Opening Br. at 40 (emphasis omitted).) They also claim that, by including misleading risk factors, Merck "blurred the relationship between Fosamax and atypical femoral fractures" in its Prior Approval Supplement. (Opening Br. at 49.) They contend that our holding in *In re: Avandia Marketing, Sales and Products Liability Litigation*, 945 F.3d 749 (3d Cir. 2019), compels us to rule for them on this prong. Merck, on the other hand, asserts that the District Court did not err because the record is clear that the FDA was fully informed and because *In re Avandia* does not support the Plaintiffs' argument.

a) The District Court did not clearly err in rejecting the Plaintiffs' argument that Merck provided misleading information to the FDA.

The Plaintiffs contend that the District Court improperly credited Merck's 2008 safety update (*see supra* Section I.C.), an important component of the Court's finding that there was "profuse evidence of information" that Merck warned the FDA about atypical femoral fractures. (J.A. at 72.) But the

Plaintiffs point to only a handful of instances that, in their view, show Merck mischaracterized the studies provided in the safety update. For example, they say that Merck improperly characterized one article by using terms and phrases like "hypothetically" and "in only few patients." (Opening Br. at 41.) They note that when Merck summarized eight other publications, it again used the word "hypothetical," which they allege was meant "to plant doubt regarding these reports' links between Fosamax and unusual fractures[.]" (Opening Br. at 42.) The Plaintiffs also quote Merck's description of one study, in which it said that "there was no evidence of increased risk of fractures associated with 10 years of treatment with alendronate and that data confirms that alendronate is safe." (Opening Br. at 43 (cleaned up).) Regarding the Prior Approval Supplement, the Plaintiffs allege that "Merck misleadingly listed risk factors (*e.g.*, abnormally decreased bone mineral density and muscle weakness) that it claimed were likely to be very important in the development of insufficiency fractures" but that were actually not. (Opening Br. at 49 (internal quotation marks omitted).)

The Plaintiffs' list of examples is thin, and their characterizations of them do not persuade us that the District Court clearly erred in finding that Merck did not mislead the FDA in its safety update and Prior Approval Supplement. Most notably, it stretches credulity to believe that Merck was attempting to mislead the FDA when, in the Prior Approval Supplement itself, the Company advocated for a new Precautions warning on the Fosamax label, explaining that, although "[i]t is not possible with present data to establish whether treatment with alendronate

increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures[,] ... it is important to include an appropriate statement ... in the product information and precautions" sections about the "need[] to identify and manage such fractures." (J.A. at 1316.)

In other words, the Plaintiffs' grievances with the safety update and Prior Approval Supplement do not establish that the District Court erred in finding that, through "formal safety updates, periodic emails, and [the Prior Approval Supplement]," Merck "clearly and fully informed the FDA of the panoply of risks associated with long-term Fosamax use and the justifications for its proposed label change." (J.A. at 70.) The District Court "culled through the extensive record" to summarize what Merck had sent the FDA prior to requesting a label change. (J.A. at 70.) It found that Merck "repeatedly and voluntarily sent relevant articles to the FDA between 1992 and 2010[,]" including the "safety update, which surveyed medical studies, journal publications, and internal data[,]" and "included numerous pages on atypical femoral fractures." (J.A. at 70.) In June 2008, Merck "promptly complied with the FDA's request for further investigations that Merck had conducted and reports Merck had received." (J.A. at 72 (internal quotation marks omitted).) Moreover, Merck's Prior Approval Supplement "not only cited nine articles reporting cases of low-energy femoral fractures in Fosamax users, but included a clinical overview in which [Merck] itself asserted a statistically significant association." (J.A. at 72.) The Court found "no basis in the record" for concluding that Merck needed to provide more information to the FDA or that what was

submitted was misleading. (J.A. at 73.) That conclusion is sound. Accordingly, the District Court did not clearly err in finding that Merck did not mislead the FDA with its submissions.[21]

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[21] The Plaintiffs also assert that Merck "hid the ball" on certain "key features" of atypical femoral fractures. (Opening Br. at 45.) For example, before the District Court, the Plaintiffs argued that Merck "did not provide the FDA with any possible pathogenesis, the manner of development of a disease, for atypical femoral fractures." (J.A. at 74.) But the Court found that "[t]he record belies this assertion" because Merck "*repeatedly* indicated how Fosamax might cause the very injury Plaintiffs suffered." (J.A. at 74.) And the Plaintiffs have no adequate response for the undisputed fact that, in clinical trials three decades ago, Merck informed the FDA that "antiresorptive agents may inhibit microdamage repair by preventing ... bone resorption at the sites of microdamage[.]" (J.A. at 74.)

The Plaintiffs further assert that Merck and the District Court "improperly conflated stress fractures with atypical femoral fractures" by "substitut[ing] 'atypical femoral' into the sentence, when context made clear Merck was discussing all low-energy fractures, including stress fractures[,]" implying that atypical femoral fractures were more common (without taking bisphosphonates) than they actually were. (Opening Br. at 47.) But we see no clear error in the District Court's finding that the safety update was not untrue or misleading in this respect. The Court explained that the warning label that the FDA created in 2010, and which is now used by Merck, "includes the observation that osteoporotic patients, generally, have suffered such fractures" without being treated by bisphosphonates like Fosamax. (J.A. at 76.) And, as Merck points out, it "said nothing [to the FDA] about [the] relative frequency" of atypical femoral fractures among those who used biphosphates and those who did not, and the "Plaintiffs do not point to anything inaccurate in Merck's submissions about the data." (Answering Br. at 30.)

b) The District Court did not clearly err in finding that Merck did not withhold any material information from the FDA.

The Plaintiffs also asserted in the District Court that Merck "deprived the FDA of relevant information between 2008 and 2009, such as information that the Task Force eventually reported, leaving the agency uncertain about the nature of atypical femoral fractures and delayed by [Merck's] inaction." (J.A. at 78 (cleaned up).) As evidence of this, they say that in April 2009, the month before the FDA issued the Complete Response Letter, the FDA emailed Merck to say that if Merck held off on its proposed amendment to the Precautions section of the label, the FDA would "work with ... Merck to decide" on "atypical fracture language ... if it is warranted." (J.A. at 1150.) According to the Plaintiffs, it is thus clear that the FDA "needed and sought more information about appropriate warning language." (Opening Br. at 50.)

The District Court found that argument "lack[ed] merit" because the "Plaintiffs do not point to any specific instance in which [Merck] failed to provide any timely and relevant information, data, case studies, or evidence to the FDA, or rebuffed a request for further engagement." (J.A. at 78.) Furthermore, the Court found that "[t]he Task Force relied on 24 new case studies and 63 new articles *after* the FDA issued its [Complete Response Letter], according to [the] Plaintiffs' own experts[,]" so it was not possible for Merck, at the time of submitting its Prior Approval Supplement, to have provided the FDA with those studies and reports. (J.A. at 79.)

On appeal, the Plaintiffs argue that the District Court "improperly shifted the burden from Merck to [the] FDA" because "[t]he standard is whether Merck fully informed [the] FDA of the justifications for an adequate warning, not whether FDA was able to ask Merck the right questions, piece together relevant data, see through Merck's obfuscations, and discern how best to draft a warning label." (Opening Br. at 51.) That argument is flawed. The District Court did not shift the burden; rather, it appropriately scrutinized the Plaintiffs' claim that Merck failed to submit additional information. Even now on appeal, the Plaintiffs do not point to what information Merck neglected to provide to the FDA. Accordingly, the District Court did not clearly err in rejecting the Plaintiffs' argument that Merck failed to provide necessary and available additional information to the FDA.

c) In re Avandia is Distinguishable.

The Plaintiffs also argue that our holding in *In re Avandia*, 945 F.3d 749, "compels reversal." (Reply Br. at 12.) In that case, we reversed a district court's order granting summary judgment in favor of a drug manufacturer that asserted an impossibility pre-emption defense. *In re Avandia*, 945 F.3d at 752.

The relevant facts were as follows. The drug manufacturer, GSK, advertised its drug, Avandia, "as being capable of both controlling a patient's blood sugar levels and reducing cardiovascular risk." *Id.* at 753 (emphasis omitted). After FDA approval, "however, concerns arose that Avandia may in fact increase certain cardiac risks." *Id.* (emphasis omitted). For that reason, GSK submitted a Prior

Approval Supplement to the FDA, requesting to add a warning to its label for those risks. *Id.* After the supplement was submitted, a new study was published about the risks of Avandia. *Id.* An FDA official told GSK that "it was difficult for FDA officials to agree on labeling language for Avandia." *Id.* at 754. "GSK's representative then proposed implementing the labelling changes" through the CBE process. *Id.* In response, "[t]he FDA official strongly advised against proceeding through the CBE process, stating that doing so may give legitimacy to [the new study] and will make people think that GSK must have other information." *Id.* (internal quotation marks omitted). The FDA sent GSK a complete response letter, stating that "the information presented [by GSK was] inadequate" and that the "data require[d] further analysis[.]" *Id.* (second alteration in original). The letter requested GSK to submit various types of specific data and information "in order to address the deficiency of [the] application." *Id.* at 758 (emphasis omitted).

Because the complete response letter "indicated that GSK needed to submit various data and information[,]" and "because the FDA itself stated that it was inadequately informed of the justifications for the warning," we concluded that "GSK could not demonstrate that the FDA was fully informed of the justifications for the warning." *Id.* (cleaned up). GSK argued that it "did not have access to the information that the FDA requested until *after* the [Agency] issued the [complete response] [l]etter[.]" *Id.* We called that argument "unavailing" because "we read *Albrecht* as holding that, in order to prove impossibility preemption, the drug manufacturer must show that

the FDA was fully informed of the justifications for the proposed warning *at the time that the FDA rejected the proposed warning*[,]" *id.* at 758-59 (cleaned up):

> In other words, [we explained,] the upshot of [*Albrecht*] is that a drug manufacturer must show that the FDA made a fully informed decision to reject a change to a drug's label in order to establish the demanding defense of impossibility preemption. If the question of whether the FDA was fully informed was not tethered in time to the question of whether the FDA indeed rejected the proposed warning, the fully informed prong of the test espoused in [*Albrecht*] would be rendered superfluous.
>
> Thus, if GSK wishes to rely on the [complete response] [l]etter as proof that the FDA rejected its proposed label change, it must also demonstrate that the FDA possessed all the information it deemed necessary to decide whether to approve or reject the proposed warning *at the time it issued the [l]etter*. By arguing that it did not have the FDA's requested data and information until *after* the FDA issued its letter, however, GSK is, in effect, conceding that the FDA was not fully informed at the time of the [l]etter's issuance. For that reason, among [] others ..., GSK cannot satisfy the first prong of the test espoused in [*Albrecht*].

Id. at 759 (internal quotation marks omitted).

The Plaintiffs argue that "*Avandia* requires the conclusion that Merck fail[ed] to show clear evidence that FDA prohibited it from adding the warning state law required[,]" reasoning that, "[a]s in *Avandia*, [the]

FDA sent a [complete response] [l]etter calling Merck's proposed 'justification' for its stress fracture language 'inadequate'" and, "[l]ike in *Avandia*, [the] FDA invited Merck to resubmit its application and to fully address all the deficiencies." (Reply Br. at 13 (internal quotation marks omitted).)

Avandia cannot be read as broadly as the Plaintiffs insist. In the Complete Response Letter that Merck received, the FDA did not request specific information, nor did it characterize as deficient the information it had received from Merck. Rather, the FDA denied Merck's Prior Approval Supplement because Merck's "justification for the proposed precautions section language [was] inadequate." (J.A. at 1152.) To say that the FDA disagrees with a proposed label change is not the same as saying there is inadequate information to make a judgment. The FDA may disagree with a proposed change for any number of reasons, including the specific wording proposed for the label. The question is not whether the FDA agrees with the drug manufacturer; the question is whether the manufacturer provided the FDA with all the relevant data and information for the FDA to make a fully informed decision. Here, the FDA did not tell Merck that it failed to provide necessary data, as it told the drug manufacturer in *Avandia*. 945 F.3d at 758. Thus, *Avandia* does not control the outcome of this case.

For all of the forgoing reasons, the District Court did not err in finding that Merck fully informed the FDA

of the justifications for adding to the Fosamax label a warning about atypical femoral fractures.[22]

2. *Prong #2: Merck Has Not Shown that the FDA Would Have Rejected Any and All Warnings that Satisfied State Law.*

The Plaintiffs argue that the District Court erred in various ways when concluding that the FDA denied Merck's label because the science did not show a sufficient causal connection between Fosamax and atypical femoral fractures. They contend that Merck proposed a warning for ordinary stress fractures rather than atypical femoral fractures. They also assert that the Complete Response Letter lacked preemptive effect so the Court should not have relied on it to find the state law claims were preempted. Even if the Letter did have preemptive effect, the Plaintiffs say, the District Court misinterpreted it because the denial was based on inadequate wording, not lack of causal evidence. They further argue that the District Court "erred in relying on informal communications" with the FDA to interpret the meaning of the Letter. (Opening Br. at 59.) Finally, they claim that Merck could have used the CBE route to change the Fosamax label and warn doctors and patients of atypical femoral fractures, contrary to the District Court's conclusion that it could not. Merck, naturally, contests all those assertions.

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[22] Because we conclude that the District Court did not err in finding that Merck fully informed the FDA of the risks of atypical femoral fractures, we do not address Merck's assertion that the Plaintiffs forfeited their argument on this point.

a) Merck offered a warning for atypical femoral fractures, not "garden-variety" stress fractures.

The Plaintiffs first argue that the District Court "missed the most fundamental point of the preemption inquiry: [the] FDA could not have informed Merck that it would disapprove a warning of atypical femoral fractures because Merck never proposed such a change." (Opening Br. at 53.) They say "the [C]ourt correctly recognized Merck's burden to establish that it" advanced a warning of atypical femoral fractures, "but erroneously concluded Merck had met its burden, despite acknowledging that Merck's warning did not employ the word 'atypical.'" (Opening Br. at 53 (internal quotation marks omitted).) In their view, the warning was one for "garden-variety" stress fractures, rather than atypical femoral fractures. (Opening Br. at 13.)

The Plaintiffs have no response to the District Court's finding that the use of "'atypical' was hardly settled scientific jargon at the time" (J.A. at 94) and thus not determinative as to the appropriate characterization of the warning. Moreover, the District Court conducted an extensive ten-page analysis explaining how Merck's proposed warning "had all the hallmarks of atypical femoral fracture such that not having employed the word 'atypical' would not somehow change the nature of the proposed warning as plainly expressed by its language." (J.A. at 94.) For example, the title of the warning itself was "Low-Energy Femoral Shaft Fracture," which refers to a fracture that results from minimal trauma to the thigh bone. (J.A. at 87-88.) The District Court found that Merck had explained in its Prior Approval

Supplement that it used the term "stress fracture" in its warning "to mean an 'insufficiency fracture' that occurs with no 'identifiable external traumatic event.'" (J.A. at 89.)

Further, the District Court found that, "regardless of any inadequacies in the text of [Merck's] warning, the FDA clearly understood the type of fracture at issue." (J.A. at 93.) As the Court noted, the FDA sent Merck a June 2008 email titled "Fosamax Information Request – Atypical Fractures," in which it asked Merck "for more data concerning the occurrence of atypical fractures." (J.A. at 93 (internal quotation marks omitted).) "What is more, the FDA even called the fractures at issue 'atypical'" in its Complete Response Letter. (J.A. at 93); (J.A. at 96 ("Identification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." (emphasis omitted) (quoting J.A. at 1152)).)

Again, the District Court's reasoning is sound. There is no legitimate basis to believe that the FDA did not understand that Merck was proposing a warning about atypical femoral fractures. The language of Merck's Prior Approval Supplement supports its position, and the plain text of the Complete Response Letter confirms that the FDA understood Merck's proposal to be one about atypical femoral fractures.

b) Complete response letters can have preemptive effect.

Before the District Court, the Plaintiffs argued that a complete response letter "does not carry preemptive effect because it is not a final agency action." (J.A. at

81.) At oral argument, the Plaintiffs conceded that complete responses letters may have preemptive effect, but they contend that the Letter in this case did not have such effect because it "invited further action" and because other FDA communications confirm its "provisional nature." (Opening Br. at 36-37.) Merck, at oral argument, conceded that not every complete response letter has preemptive effect, but it argues that the Letter in this case did. Thus, on appeal, the parties are in accord that the particular language of a complete response letter governs its preemptive effect.

We too agree. The Supreme Court "has recognized that an agency regulation with the force of law can pre-empt conflicting state requirements." *Wyeth*, 555 U.S. at 576. In *Albrecht*, the Court stated that "[f]ederal law permits the FDA to communicate its disapproval of a warning" "by formally rejecting a warning label that would have been adequate under state law[.]" *Albrecht*, 587 U.S. at 315-16. The Court cited § 314.110(a), the regulation setting forth the rules regarding complete response letters, for that statement. *Id.* at 316. Although the Supreme Court's statement was dicta because, as it recognized, "[t]he question of [a] disapproval 'method' [was] not ... before [it,]" we do not take lightly the Court's citation to the regulation governing complete response letters as an example of an "agency action[] that can determine the answer to the pre-emption question[.]"[23] *Id.* at 315-16.

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[23] The Plaintiffs relied on Justice Thomas's concurrence in *Albrecht* (*see supra* note 13) where he held that complete response letters "cannot be 'Law' with pre-emptive effect" because they "merely 'infor[m] sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application[.]'" 587 U.S. at 322

The bottom line is that a complete response letter may have preemptive effect, but whether it does depends upon the specific language it uses.

c) The District Court erred in concluding that the FDA would have rejected any and all labels that would have satisfied state law.

The outcome of this case thus largely depends on the interpretation of the Complete Response Letter the FDA issued to deny Merck's Prior Approval Supplement. The paragraph in the Letter explaining the FDA's reasons for denying Merck's proposed label change is, again (*see supra* Section I.C.), as follows:

> While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

(J.A. at 1152-53.)

Not surprisingly, the parties diverge in their interpretation of that paragraph. "In Merck's view, the FDA concluded that the science did not yet show a sufficiently clear connection to justify a warning, and

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(Thomas, J., concurring) (emphasis omitted) (quoting 73 Fed. Reg. at 39589). The majority, however, did not adopt his view.

thus the [A]gency would not approve a change to the drug's label to include that warning." (Answering Br. at 36 (cleaned up).) In contrast, the Plaintiffs theorize that the "FDA's critique was not that the 'literature' insufficiently linked Fosamax to atypical femoral fractures; it was that Merck's discussion of 'stress fractures' misidentified the risk." (Opening Br. at 57.)

The District Court itself thought the Letter to be ambiguous. It explained that, "as worded, the language of the [Complete Response Letter] gives rise to competing inferences with respect to why the FDA rejected [Merck]'s warning." (J.A. at 96.) "On the one hand," the Court said, the Letter "describes the 'justification' for the warning as 'inadequate[,]'" so, "[l]ogically, the [Letter] was presumably referencing the data [Merck] submitted with its [Prior Approval Supplement], linking low-energy femur fractures to bisphosphonates." (J.A. at 96.) The Court continued, "[o]n the other hand, the [Letter] discusses [Merck]'s use of the term 'stress fracture,' stating that such fractures 'may not be clearly related to the atypical ... fractures that have been reported in the literature' and it is 'not warranted' to discuss risk factors for them." (J.A. at 96-97.)

The District Court acknowledged that "[i]f the [Complete Response Letter] were the sum total of the evidence of FDA action in this case, [the] Plaintiffs might be on firmer footing with regards to their preemption arguments." (J.A. at 97.) But the Court continued: "Focusing on the sequence of communications and announcements from the same period, the [Letter] does not tell the whole story without the proper context gleaned from other FDA communications." (J.A. at 99.) "In light of [the]

competing readings, [the District Court] … look[ed] beyond the [Letter]'s terms alone to ascertain its meaning and scope." (J.A. at 97.) The Court recognized that "informal communications do not constitute 'Laws' with the power to preempt[,]" but believed it was appropriate to use those communications for the "limited purpose" to "'shed light on' the meaning and scope of the [Complete Response Letter], which is 'Law' with preemptive effect." (J.A. at 98 (emphasis omitted).)

First, the District Court looked at certain phone call notes (described *supra* Section I.C.) that were prepared by a Merck employee, regarding a conversation that took place between Merck and the FDA one month before the Complete Response Letter was issued. According to those notes, the FDA representative indicated that "[t]he conflicting nature of the literature [did] not provide a clear path forward, and more time [would] be need[ed] for FDA to formulate a formal opinion on the issue of a precaution around these data." (J.A. at 1251.) The Court then referred to the FDA's March 2010 Safety Announcement, which stated that the FDA's "review of the data 'did not show an increase in th[e] risk' of atypical femoral fractures from bisphosphonate use." (J.A. at 97 (quoting J.A. at 1160)). "FDA officials did not change their assessment[,]" the Court noted, "until October 2010, a month after the Task Force issued its Report[.]" (J.A. at 97).

The District Court also relied on an amicus brief the FDA filed in *Albrecht*, in which the Agency asserted that "it rejected [Merck]'s warning for 'the lack of adequate data to support [it],' and not 'because of ... the term 'stress fractures.'" (J.A. at 101 (alterations in

original).) The Court believed that the FDA's own interpretation of its Complete Response Letter "deserve[d] some measure of deference." (J.A. at 102 (citing *Auer v. Robbins*, 519 U.S. 452, 461-62 (1997)).) It reasoned that it was "appropriate to consider the FDA's views because Congress delegated to that agency the authority to implement federal drug regulations, it has expertise in that highly 'technical' subject matter, and it is well-equipped to navigate 'the relevant history and background' on such a 'complex and extensive' issue."[24] (J.A. at 102 (quoting *Geier v. American Honda Motor Co.*, 529 U.S. 861, 883 (2000)).)

The District Court concluded that, when "[c]onstrued in light of these various FDA communications, the [Complete Response Letter] clearly rejected [Merck]'s warning, in part, because the FDA doubted the underlying science causally connecting bisphosphonate use and atypical femoral fractures." (J.A. at 101.) Accordingly, the Court was "satisfied that the evidence is clear and convincing that the Agency would not have approved a differently worded warning no matter how Defendant attempted to submit one." (J.A. at 123.)

Merck argues that the Court's conclusion that the FDA denied Merck's application for scientific reasons constitutes a factual finding that we must review for clear error. Not so. Written instruments, "such as

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[24] The District Court noted its awareness "that in *Kisor v.* [*Wilkie*], [588 U.S. 558] (2019), the Supreme Court warned that 'a court should decline to defer to a merely convenient litigation position or post-hoc rationalization advanced to defend past agency action against attack,' such as a brand-new interpretation presented for the first time in legal briefs." (J.A. at 102 (quoting *Kisor*, 588 U.S. at 579 (cleaned up)).)

those normally produced by a federal agency to memorialize its considered judgments[,]" *Albrecht*, 587 U.S. at 316, like the Complete Response Letter in this case, "often present[] a question solely of law, at least when the words in those instruments are used in their ordinary meaning[,]" *Teva*, 574 U.S. at 326 (internal quotation marks omitted).[25] Indeed, the question of agency disapproval "often involves the use of legal skills to determine whether [the] disapproval fits facts that are not in dispute." *Albrecht*, 587 U.S. at 316. The "meaning and effect of an agency decision" is a "legal determination[.]" *Id.* at 317. Therefore, the interpretation of the Complete Response Letter is a question of law that we review de novo.

We agree with the District Court that the Letter's language is ambiguous. The FDA told Merck that the proffered "justification for the proposed precautions section language is inadequate." (J.A. at 1152 (cleaned up).) The word "justification" could be referring to a lack of scientific support showing a connection between Fosamax and atypical femoral fractures. But it could also mean that there is no basis to include language referring to generic stress fractures in a warning that is supposed to be about atypical femoral

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[25] It is true that "technical words or phrases not commonly understood ... may give rise to a factual dispute" and that resolution of those factual disputes is reviewed for clear error. *Teva*, 574 U.S. at 326 (citation and internal quotation marks omitted). But the District Court's conclusion in this case did not depend on the meaning of any technical words and phrases in the Complete Response Letter. Rather, the Court concluded, based on informal communications and the FDA's amicus brief, that the reason the FDA denied Merck's Prior Approval Supplement must have been because of lack of scientific evidence.

fractures. The FDA then noted that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature" and that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." (J.A. at 1152-53.) Those statements may be a clarification of why the "justification" for the label was deemed lacking – the term "stress fractures" does not convey the same meaning as "atypical femoral fractures." But the FDA may have also been communicating a second, independent reason the label was rejected, in addition to a lack of scientific evidence.

Undertaking our own review of the Complete Response Letter in the context of the pre-emption question presented here, we conclude that the District Court erred by placing too much weight on informal FDA communications and the Agency's amicus brief to decide that the Letter preempted the Plaintiffs' state law claims. We acknowledge that this is a close case, but, in a close case, the strong presumption that the Supreme Court has established will likely be determinative. The "difficult" and "demanding" clear-evidence standard is one that "a drug manufacturer will not ordinarily be able to show[.]" *Albrecht*, 587 U.S. at 313, 315. Congress's intent to preserve state law claims in the drug labeling context would be undermined, and the presumption against pre-emption that exists in that context would have diminished effect, if the kinds of informal communications the District Court relied on here could readily serve as the determinative evidence in answering the pre-emption question.

Again, "the purpose of Congress is the ultimate touchstone in every pre-emption case." *Wyeth*, 555 U.S. at 565. In the drug labeling context, Congress has repeatedly "[taken] care to preserve state law" because it "determined that widely available state rights of action provide[] appropriate relief for injured consumers" and because "state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id.* at 567, 574. And the Supreme Court, after undertaking "a careful review of the history of federal regulation of drugs and drug labeling[,]" "found nothing within that history to indicate that the FDA's power to approve or to disapprove labeling changes, by itself, pre-empts state law." *Albrecht*, 587 U.S. at 311.

> Rather, [the Court] 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 "aware 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."

Id. (cleaned up) (quoting *Wyeth*, 555 U.S. at 574-75).

The Supreme Court has "also observed that, '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.'" *Id.* at 312 (quoting *Wyeth*, 555 U.S. at 570-71). Accordingly, we must view the pre-emption question here "[i]n light of Congress' reluctance to displace state laws that would penalize drug manufacturers for failing to warn consumers of the risks associated with their drugs, and Congress' insistence on requiring drug manufacturers to bear the responsibility for the content of their drug labels[.]" *Id.*

We are not unsympathetic to the pressures Merck faced from the competing demands of a possible state law requirement and FDA action, but there is no escaping the consequences of *Albrecht*. The Supreme Court has established a very high bar to show impossibility pre-emption in drug labeling cases. It is Merck's burden to show that "federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding *any and all* warnings to the drug label that would satisfy state law." *Albrecht*, 587 U.S. at 313-14 (emphasis added). And because "federal law – the FDA's CBE regulation – permits drug manufacturers to change a label ... without prior approval from the FDA[,]" "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."[26] *Id.* at 314-15.

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[26] While the FDA's CBE regulation can permit a drug manufacturer to unilaterally change its drug label without prior FDA approval, analogous procedures do not necessarily exist in other product labeling contexts, and that difference can matter in a pre-emption analysis. In our recent decision in *Schaffner v. Monsanto Corp.*, the plaintiffs alleged that a pesticide producer violated Pennsylvania state law by omitting a required cancer warning from the label of its weed-killer product. No. 22-3075,

Merck must show that the "federal and state laws *irreconcilably conflict*." *Id.* at 315 (internal quotation marks omitted) (emphasis added). In short, we are bound to consider the "presumption against pre-emption" when analyzing the particular Complete Response Letter in this case. *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005). We actually "have a duty to accept the reading that disfavors pre-emption." *Id.*

---F.4th ----, 2024 WL 3820973, at *1 (3d Cir. 2024). The applicable federal statute in that case – the Federal Insecticide, Fungicide, and Rodenticide Act – contains an express pre-emption clause that overrides any state-law pesticide labeling requirement differing from the requirements of federal law. *See* 7 U.S.C.A. § 136v (States "shall not impose or continue in effect any requirements for labeling or packaging in addition to or different from those required under this subchapter."). The regulations promulgated under that statute provide that, barring certain exceptions, pesticide producers cannot change a product's labels unless the Environmental Protection Agency approves the change in advance. *See* 40 C.F.R. § 152.44(a) ("If an application for amended registration is required, the application must be approved by the Agency before the product, as modified, may legally be distributed or sold.").

The statutory and regulatory regime in that case is thus quite different from the one we are dealing with here. As noted previously (*see supra* Section I.A.1.), Congress has not set forth an express pre-emption provision in the drug labeling context. And the Supreme Court has said that nothing in the legislative history of the FDCA shows "that the FDA's power to approve or to disapprove labeling changes, by itself, pre-empts state law." *Albrecht*, 587 U.S. at 311. Unlike in the pesticide labeling context, drug manufactures may have opportunities to unilaterally change their products' labels prior to receiving agency approval. Thus, our decision in *Schaffner* does not dictate the pre-emption analysis in this case.

That is why, despite the superb work of the District Court, we believe it erred. It did not read the FDA's Complete Response Letter in a manner that disfavors pre-emption and carries out Congress's intent to permit displacement of state law only when it is abundantly clear that it is impossible for a manufacturer to comply with both federal and state law.[27] The "possibility" that the Letter communicated

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[27] Admittedly, after the Supreme Court vacated our *Fosamax I* decision (*see supra* Section I.D.3.), we instructed the District Court "to determine the effect of the [FDA]'s Complete Response Letter ... and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." (J.A. at 38 (quoting Order at 1, *In Re: Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, No. 14-1900 (3d Cir. Nov. 25, 2019)).) That instruction may have misled the District Court to think the extrinsic evidence in this case could be determinative. While we cannot exclude the possibility that extrinsic evidence may prove helpful in some future case, it cannot be determinative in a case like this, where the ambiguities in the FDA's Complete Response Letter are swept away by the heavy *Albrecht* presumption. Given how emphatically the Supreme Court has directed our attention to the weight of that presumption, it appears that ambiguity alone will seldom, if ever, be enough to overcome the presumption.

But even if it had been necessary to consult extrinsic evidence to answer the legal question in this case, it is not clear that the evidence helps Merck. For example, the District Court relied on the call notes from April 2009 in which Merck discussed with FDA officials its pending request to change the Fosamax label. While the call notes suggest that the FDA indicated "the conflicting nature of the literature [did] not provide a clear path forward" at that time, it did not foreclose the possibility that there was enough scientific evidence of a connection between bisphosphonates and atypical femoral fractures to add a warning to the Precautions section of the Fosamax label. In fact, the FDA said only that it needed "more time" to "formulate a formal opinion on the issue of a precaution around these data." (J.A. at

a conflict between federal and state law "is not enough."[28] *Albrecht*, 587 U.S. at 314 (cleaned up).

1251.) And the FDA's suggestion that Merck amend only the Adverse Reactions section of the Fosamax label was proposed only as "an interim measure[.]" (J.A. at 1250.)

The only clear extrinsic evidence that the District Court relied on consisted of the Agency's statements in an amicus brief in *Albrecht* that the proposed label change was rejected because the science did not show a sufficient connection between Fosamax and atypical femoral fractures. Although "we presume that Congress intended for courts to defer to agencies' reasonable readings of genuinely ambiguous regulations" in some circumstances, *Kisor v. Wilkie*, 588 U.S. 558, 563 (2019) (citing *Auer*, 519 U.S. at 461-62), "such a presumption cannot always hold." *Id.* (citing *City of Arlington v. FCC*, 569 U.S. 290, 309-10 (2013) (Breyer J., concurring in part and concurring in judgment). And, in this particular context, the Supreme Court has declared that "agencies have no special authority to pronounce on pre-emption absent delegation by Congress" and we do "not defer[] to an agency's conclusion that state law is pre-empted." *Wyeth*, 555 U.S. at 576-77 (emphasis omitted). Deferring to the FDA's post-hoc assertion about the Complete Response Letter would effectively give the FDA the power to decide the pre-emption question we are responsible to answer. *Id.*; *Albrecht*, 587 U.S. at 316 ("concluding that the question is a legal one for the judge"); *cf. Loper Bright Enters. v. Raimondo*, 144 S. Ct. 2244, 2267 (2024) ("[W]hen an ambiguity happens to implicate a technical matter, it does not follow that Congress has taken the power to authoritatively interpret the statute from the courts and given it to the agency. Congress expects courts to handle technical statutory questions.").

[28] With the words "possibility" and "not enough," we are again confronted with the "is it a question of law or fact" conundrum. The Supreme Court recognized in *Albrecht* that the issue of pre-emption is not a pristine question of law, that it is instead a question that may involve "contested brute facts." 587 U.S. at 317. The Court nonetheless endeavored to push the issue as far toward the "question of law" end of the spectrum as it could. In light of *Wyeth* and *Albrecht*, however, it is hard to avoid the

conclusion that facts will often abound in these labeling cases, both when asking what the drug manufacturer did to inform the FDA of justifications for adding a new warning to a drug's label and when asking whether "the FDA would not approve changing the drug's label to include that warning." *Id.* at 314. The first of those questions requires an inquiry into historical fact. The second may well invite consideration of a hypothetical future. When one asks, "would you or would you not approve this change" there is a foray into facts, albeit conjectural facts in the future. The potentially sweeping nature of that inquiry is emphasized by the Supreme Court's further statement that the drug manufacturer must show that "federal law prohibited [it] from adding *any and all* warnings ... that would satisfy state law. *Id.* at 313-14 (emphasis added). That invokes a broad array of possibilities.

True enough, *Albrecht* can be read as framing the inquiry in terms of comparing federal law and state law and looking for an overlap that can accommodate an appropriate drug warning. That looks like pretty pristine legal work. But since the question a drug manufacturer faces first is not what its lawyers make of legal texts but what the FDA makes of them, and since an agency's policies can and sometimes do vary from administration to administration, the issue starts to look a good deal less than pristinely legal. As soon as one asks what the FDA would or would not do, one is confronted with figuring out just how much proof – regardless of whether a judge is making the assessment instead of a jury – is enough to persuade the decisionmaker of what that hypothetical future looks like. Thus, while the opinion in *Albrecht* declined to "further define *Wyeth*'s use of the words 'clear evidence' in terms of evidentiary standards, such as 'preponderance of the evidence' or 'clear and convincing evidence' and so forth," *id.* at 315, it still asks courts to hold drug manufacturers to some standard of proof. It is not easy to get away from *Wyeth*'s statement, not disclaimed in *Albrecht*, that "clear evidence" is required. *Wyeth*, 555 U.S. at 571 (quoted in *Albrecht*, 587 U.S. at 313). As discussed, *Albrecht* defines "clear evidence" as "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

Although it is possible that, had Merck suggested an atypical femoral fracture label, the FDA would have prohibited it, "[t]he existence of a hypothetical or potential conflict is insufficient to warrant the pre-emption of the state statute." *Rice*, 458 U.S. at 659. To support the conclusion that there was pre-emption, the FDA, acting with the force of law, must have clearly rejected Merck's label in a manner that made it evident that no label about atypical femoral fractures would have been appropriate at the time of Merck's Prior Approval Supplement. That did not happen here. For that reason, Merck has not shown that the FDA would have rejected any and all labels that would have satisfied state law. In addition, the availability of a label change via a CBE supplement is problematic for Merck, as will very often be the case for pharmaceutical companies raising an impossibility defense.[29] The bar set by *Albrecht* is high indeed. Therefore, Merck has not shown that federal and state law irreconcilably conflict.[30]

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a change to the drug's label to include that warning." 587 U.S. at 303. That is the standard we are endeavoring to apply here.

[29] As a reminder (*see supra* Section I.A.3.), a drug manufacturer cannot use a CBE supplement to make a major change to a drug's label. Instead, it must use a Prior Approval Supplement to do so. § 314.70(b). For that reason, the CBE regulation is not relevant to the preemption analysis for any major changes made to a drug's label.

[30] We are not deciding whether "there is sufficient evidence to find that Merck violated state law by failing to add a warning about atypical femoral fractures to the Fosamax label." *Albrecht*, 587 U.S. at 314. That conclusion must be determined at trial. Nor are we implying anything about the evidence that will be admissible at trial. Our holding is solely that the Plaintiffs' state law claims are not preempted.

d) The Statutory and Regulatory Framework Does Not Change Our Conclusion.

(1) Section 355(o)(4)(A)

Merck relies on § 355(o)(4)(A), which, in his concurring opinion in *Albrecht*, Justice Alito noted we would do well to consider on remand. (*See supra* note 14.) We do so now. Under that provision, the FDA has a duty to notify drug manufacturers if it "becomes aware of new information" that "should be included in the labeling[.]"[31] § 355(o)(4)(A). After discussions with the manufacturer, the Agency "may issue an order directing" the manufacturer "to make such a labeling change as the [FDA] deems appropriate to address the new safety or new effectiveness information." § 355(o)(4)(E). Merck argues that it "strains credulity to claim the FDA did not agree with Merck's use of 'stress fracture' terminology and therefore did nothing – even at the expense of patient safety." (Answering Br. at 40.) That echoes Justice Alito's comment that § 355(o)(4)(A) "arguably affect[s] the pre-emption analysis" "because, if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *Albrecht*, 587 U.S. at 324 (Alito, J., concurring). He suggested that FDA inaction could communicate disapproval of a warning because § 355(o)(4)(A) does not "require the FDA to

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[31] We agree with the parties that § 355(o)(4)(A) is relevant to the second prong of the *Albrecht* analysis – i.e., whether the FDA informed Merck that it would not have accepted any label about atypical femoral fractures that satisfies state law.

communicate to the relevant drug manufacturer that a label change is unwarranted; instead, the FDA could simply consider the new information and decide not to act." *Id.* at 325.

No doubt § 355(o)(4)(A) may prove important when the FDA has "received *and considered* information regarding a new risk[.]" *Id.* at 324 (emphasis added). But, in this case, it appears that the FDA had not fully considered the information that Merck and other bisphosphonate manufacturers had submitted prior to issuing the Complete Response Letter to Merck. If one assumes that the FDA's refusal was based only on the lack of a satisfactory link between Fosamax and atypical femoral fractures, then the suggestion that a warning could be added to the Adverse Reactions section of the label but not the Precautions section can be seen as a statement by the FDA that it was not fully convinced of the link *yet*, not that it could not be convinced.

And if one looks beyond the Letter, it is more apparent that the FDA was still assessing evidence. As earlier discussed (*see supra* Section I.C.), in April 2009, a Merck representative had a phone conversation with FDA officials about the pending request to change the Fosamax label. On that call, Merck explained to the FDA that it "was anxious to understand [the] FDA's timelines for completing their review of [the Fosamax Prior Approval Supplement] and that this information had not been forthcoming[.]" (J.A. at 1251.) The FDA officials explained that the Agency's "duration of review was related to [Merck's] elevation of [the atypical femoral fractures] issue to a precaution in the labeling." (J.A. at 1251.) They "indicated that they could *agree quickly* to language in

the [Adverse Reactions] section of the labeling[,] but that the Agency "would like to approach the issue of a precaution from the [perspective] of all bisphosphonates" and was working to do so. (J.A. at 1251 (emphasis added).) According to the call notes, "the conflicting nature of the literature [did] not provide a clear path forward, [so] *more time [was] need[ed]* for [the] FDA to formulate a formal opinion on the issue of a precaution around these data." (J.A. at 1251 (emphasis added).) Again, the FDA suggested that, "as an *interim measure*," Merck could amend the Adverse Reactions section of the Fosamax label. (J.A. at 1250 (emphasis added).) In a follow-up email, the FDA told Merck that it would "work with [the Agency's Office of Surveillance and Epidemiology] and Merck to decide on language" for the Warnings and Precaution section, "*if it is warranted*." (J.A. at 1150 (emphasis added).)

Those undisputed facts indicate that, when the FDA issued the Complete Response Letter in May 2009, it had not yet determined whether a change to the Precautions section of the label was warranted. It was not until the Task Force report issued in September 2010 that the FDA decided it had enough information to use its authority under § 355(o)(4)(A) to require Merck and other bisphosphonate manufacturers to include a warning about atypical femoral fractures in the Precautions section of the label. So, while § 355(o)(4)(A) is relevant to the pre-emption analysis when the FDA has fully considered the information submitted by a drug manufacturer, it does not change our analysis in this case because the FDA was in the process of deciding whether a change to the

Precautions section of the label was needed at the time it issued the Complete Response Letter.[32]

Whether it seems fair or not, the FDA can take its time, but Merck is responsible "for the content of its label at all times." *Albrecht*, 587 U.S. at 312. Practical considerations are a factor in laying that continuing responsibility on the drug manufacturer. "The FDA has limited resources to monitor the ... drugs on the market, and manufacturers have superior access to information about their drugs, especially … as new risks emerge." *Wyeth*, 555 U.S. at 578-79. "State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly." *Id.* "They also serve a distinct compensatory function that may motivate injured persons to come forward with information." *Id.* In short, "[f]ailure-to-warn actions," like this case, "lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id.*; *see also* § 355(o)(4)(I) ("This paragraph shall not be construed to affect the responsibility of the [drug manufacturer] … to maintain its label in accordance with existing requirements[.]"). Thus, since the FDA had not

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[32] Analyzing the informal FDA communications to determine the impact of § 355(o)(4)(A) in this case is not inconsistent with our previous conclusion that the District Court erred in relying too heavily on such communications to answer the preemption question. We must "understand and … interpret agency decisions in light of the governing statutory and regulatory context." *Albrecht*, 587 U.S. at 316. We do not analyze the FDA communications here to interpret the Complete Response Letter; we look at them only to determine whether § 355(o)(4)(A) has some importance in this particular case.

formalized a decision on whether to include atypical femoral fracture language in the Precautions section of Fosamax's label, it is not dispositive that the Agency did not invoke its power under § 355(o)(4)(A) to require manufacturers to change its label.

(2) Section 314.105(b)

Merck also argues that § 314.105(b) of the FDA's regulations "bolsters the inference that the FDA did not believe there was reasonable scientific evidence of a causal association between bisphosphonate use and atypical femoral fractures[.]" (Answering Br. at 40 (internal quotation marks omitted).) That provision states the FDA will approve a drug application "if the only deficiencies in the [application] concern editorial or similar minor deficiencies in the draft labeling." § 314.105(b). Thus, according to Merck, if the FDA had a problem with the "stress fracture" language, it "could have simply stricken it, as it did two years later, or approved it on the condition that [Merck] implement edits." (Answering Br. at 40 (alteration in original).)

That argument has some persuasive force if one accepts that the "stress fracture" language in the proposed warning was viewed as merely a poor choice of words. We have our doubts about that premise. All but the first sentence of the proposed Precautions warning used the term "stress fracture," and that emphasis may well have been significant to the FDA.[33]

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[33] As a reminder (*see supra* Section I.C.), the proposed Precautions warning states:

> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress

(*See* J.A. at 1280.) After all, the regulations provide that the FDA will use a complete response letter to deny an application if the drug's "proposed labeling is false or misleading in *any particular*." § 314.125(b)(6) (emphasis added); § 314.110(a) (The "FDA will send the applicant a complete response letter if the [A]gency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively."). So it may be that the Plaintiffs are correct in their assertion that the FDA denied the labeling change because the stress fracture language was viewed as misleading. Ultimately, the statutory and regulatory provisions that Merck cites do not change our conclusion that the Plaintiffs' state law claims are not preempted.

> fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.
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> (J.A. at 1280.)

III. CONCLUSION

For the foregoing reasons, we will vacate the District Court's judgment and remand the case for further proceedings.[34]

[34] Our opinion today analyzes drug labeling in the brand-name drug manufacturer context. The statutory and regulatory regime is different for generic drug manufacturers. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 626 (2011) ("[T]he federal statutes and regulations that apply to brand-name drug manufacturers are meaningfully different than those that apply to generic drug manufacturers."). We do not opine on the principles to be applied in that different context.

APPENDIX B

FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION	MDL No. 2243
THIS OPINION RELATES TO: ALL ACTIONS	Civil Action No. 3:08-08 (FLW)
	OPINION

WOLFSON, Chief Judge:

In this failure-to-warn case, more than 500 individuals ("Plaintiffs") who took Fosamax, a drug manufactured by Defendant Merck Sharp & Dohme ("Defendant" or "Merck") to prevent and treat osteoporosis in postmenopausal women, brought suit claiming that they suffered atypical femoral fractures between 1999 and 2010. More than eight years ago, following a bellwether trial, the late Hon. Joel A. Pisano, U.S.D.J., granted summary judgment in favor of Merck, ruling that federal law preempted Plaintiff's state law failure-to-warn claims.[1] *In re Fosamax*

[1] After Judge Pisano retired from the Court, the Multidistrict Litigation Panel reassigned this MDL to me.

(Alendronate Sodium) Prod. Liab. Litig., 951 F. Supp. 3d 695, 701, 703-04 (D.N.J. 2013) [hereinafter *Glynn*]. On appeal, the Third Circuit vacated and remanded this matter, concluding that preemption presented "a question of fact for the jury," not a question of law for the judge. *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 852 F.3d 268, 271, 293 (3d Cir. 2017) [hereinafter *Fosamax*], *vacated and remanded*, 139 S.Ct. 1668. And, in answering that question, the Third Circuit held that the jury must apply a heightened standard of proof, sustaining the preemption defense only if Merck proved it by "clear and convincing evidence." *Id.* at 285-86. Merck, however, petitioned for a writ of certiorari, which was granted by the United States Supreme Court. In *Merck Sharpe & Dohme Corp. v. Albrecht*, 139 S.Ct. 1668, 1676, 1679-80 (2019), the Supreme Court vacated and remanded the Third Circuit's decision, holding that the preemption inquiry is "a legal one for the judge, not a jury." Upon remand, the Third Circuit returned the case to this Court to decide "in the first instance whether the plaintiffs' state law claims are preempted by federal law under the standards described by the Supreme Court." Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019). The Third Circuit further instructed this Court "to determine the effect of the [Food and Drug Administration's ("FDA" or "Agency")] Complete Response Letter [("CRL")] and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." *Id.*

On remand, Merck reiterates its position that federal law preempts Plaintiffs' state law failure-to-warn claims. In particular, Defendant relies on the FDA's 2019 communication, in the form of a CRL,

rejecting a warning concerning atypical femoral fractures that Merck proposed. Plaintiffs, on the other hand, argue that the CRL is not "clear evidence" that the FDA would have rejected any and all warnings. Having reviewed the submission of the parties, the Court finds that based on clear and convincing evidence, Defendant fully informed the FDA of the justifications for its proposed warning, which was adequate under state law and encompassed the injury Plaintiffs allege here, and the FDA, in turn, informed Defendant that it would not approve changing the Fosamax label to include that warning in the CRL. Because the FDA's rejection was predicated on insufficient evidence of a causal link between Fosamax and atypical femoral fractures, it is clear that the Agency would not have approved a differently worded warning about such a risk. Plaintiffs' state law failure-to-warn claims are therefore preempted, and Defendant's Motion for Summary Judgment is **GRANTED**.

FACUAL BACKGROUND AND PROCEDURAL HISTORY

The factual background and procedural history of this case, which are largely not in dispute, are primarily adopted from the Supreme Court and Third Circuit's decisions in this matter, as well as Judge Pisano's dual decisions in *Glynn* and *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 2014 WL 1266994, at *17 (D.N.J. Mar. 22, 2014) [hereinafter *OTSC Opinion*].

A. *Fosamax*

Merck manufactures Fosamax, a drug that treats and prevents osteoporosis in postmenopausal women.

Merck, 139 S.Ct. at 1668. Fosamax belongs to a class of drugs called "bisphosphonates," which operate on the "remodeling process," where the body breaks down bones and builds them back up. In postmenopausal women, this process can "fall out of sync," *id*. at 1673, such that the body removes old bone cells faster than it replaces them. When resorption exceeds formation, the result is osteoporosis, or low bone mass that increases the risk of fractures. Fosamax "slows the breakdown of old bone cells and thereby helps postmenopausal women avoid [such] fractures." *Id*. However, by reducing resorption, the drug may cause some microscopic stress fractures to develop into a specific type of stress fracture known as atypical femoral fractures, or complete breaks that "cause great pain and require surgical intervention to repair." *Id*. at 1674.

A low energy, or also known as atypical, fracture is defined as one that is caused by the equivalent of a fall from standing height or less, which involves minimal force. A stress fracture is defined as a partial or complete fracture occurring with either normal or increased activity, but without an identifiable external traumatic event. Stress fractures, in this context, are included in the larger group of low-energy fractures. In postmenopausal osteoporotic women, the proximal femur is one of the most commonly affected sites for fractures, as are the pelvis, distal tibia and metatarsals. *See* Def. Br., Ex. 1 at A2751-52.

B. *The Regulatory Framework for Drug Labeling*

Congress has charged the FDA with ensuring that every prescription drug on the market is "safe for use under the conditions prescribed, recommended, or

suggested" in its "labeling." 21 U.S.C. § 355(d). As that directive suggests, labeling is the "centerpiece" of the FDA's risk management strategy for approved drugs, and the primary means by which the FDA communicates its conclusions about drug safety to the public. 71 Fed. Reg. 3922, 3944. Prospective drug manufacturers, such as Merck, must work with the FDA to develop an appropriate label when they submit a new drug for approval. 21 U.S.C. §§ 355(a), (b), (d)(7); 21 C.F.R. § 314.125(b)(6). The FDA closely regulates the safety information on drug labels, down to the exact text of warnings.[2] 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 201.57(a).

Drug labels include two sections relevant to this case: a "Precautions" section and an "Adverse Reactions" section. The Precautions section narrowly describes "clinically significant adverse reactions," including any that are "serious even if infrequent." 21 C.F.R. § 201.57(c)(6)(i). The Adverse Reactions section more broadly describes "the overall . . . profile of the drug based on the entire safety database," including a

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[2] In this context, the label "refers more broadly to the written material that is sent to the physician who prescribes the drug and . . . that comes with the prescription bottle when the drug is handed to the patient at the pharmacy." *Merck*, 139 S.Ct. at 1672; 21 U.S.C. § 321(m). The label contains detailed information about the drug's medical uses and health risks. 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 201.57(a). The FDA regulates the content, format, and order of the safety information on the drug label. 21 C.F.R. § 201.57(c). Drug labels must include, *inter alia*, warnings and precautions about potential safety hazards and adverse reactions for which there is sufficient evidence of, as determined by the FDA, a causal relationship between the drug and the occurrence of the adverse event. *See infra*.

list of all "undesirable effect[s], reasonably associated with use." *Id.* § 201.57(c)(7).

The threshold for placing a warning regarding an adverse event in the Precautions section is "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6)(iii) (providing that the Precautions section "must be revised to include a warning about a clinically significant hazard as soon as there is [such evidence] . . . a causal relationship need not have been definitely established"); Fed. Reg. 49,603, 49,604. The FDA designed this standard so as not to dilute "more important warnings" or "deter appropriate use." 73 Fed. Reg. at 49,605, 40,606. In other words, the Precautions section is reserved for a "discrete set" of serious risks that would affect a doctor's prescribing decisions or be "potentially fatal." 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). On the other hand, the threshold for warning of an adverse event in the Adverse Reactions section is comparatively lower: "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7).

New information about a drug may require changing its label. 21 U.S.C. §§ 314.80(c), 314.81(b)(2)(i). A drug manufacturer may change its label in one of two ways. More commonly, it may seek advance permission from the FDA through a Prior Approval Supplement Application ("PAS"). 21 C.F.R. § 314.70(b). Alternatively, it may change a label immediately and unilaterally through a Changes

Being Effected Application ("CBE") to reflect "newly acquired information" about "evidence of a casual association between the drug and a risk of harm." *Merck*, 139 S.Ct. at 1673 (quotations omitted); 21 U.S.C. § 314.70(c)(6)(iii)(A); 21 C.F.R. § 314.3(b) (defining "[n]ewly acquired information" to mean, *inter alia*, risks not previously known or previously underestimated). Whatever method a manufacturer chooses, it must meet the causal thresholds described above, and significantly, the FDA retains authority to reject even a CBE amendment if there is insufficient evidence of a link between the drug and the adverse event. 73 Fed. Reg. 2848, 2851; 21 C.F.R. § 314.70(c)(6)(iii)(A) (providing that the FDA will approve a label change only if "the evidence of a causal association satisfies the standard for inclusion in the labeling"); *id.* §§ 314.125(b)(6), (b)(8).

Because of the availability of the CBE process, "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." *Merck*, 139 S.Ct. at 1679. At the same time, the FDA will not approve a warning simply out of an abundance of caution whenever a manufacturer posits an association between a drug and an adverse event. As the FDA has long recognized, "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug." 73 Fed. Reg. 2848, 2851. Because "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance," the FDA prohibits "a change to labeling [, either through the PAS or CBE process,] to add a [Precautions] warning in the absence

of [at least] reasonable evidence of an association." *Id*. This represents a more conservative approach than state tort law, which generally incentivizes a manufacturer to warn about every conceivable hazard to limit liability. *See Wyeth v. Levine*, 555 U.S. 555, 557 (2009).

Finally, the FDA has an independent obligation to ensure that drug labels reflect new risks. 21 U.S.C. § 355(o)(4)(A) (providing that, if the agency "becomes aware of new information, including any new safety information," which "should be included in the labeling of the drug," it "shall promptly notify the [manufacturer]"). Indeed, Congress has "reaffirmed the manufacturer's . . . ultimate responsibility for its label," including when it "granted the FDA th[e] authority" to mandate label changes in 2007.[3] *Wyeth*, 555 U.S. at 571; 21 U.S.C. § 355(o)(4)(I). If new safety information arises regarding a particular risk, the

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[3] FDA regulations also require a New Drug Application ("NDA") to disclose all "pertinent" safety information. 21 C.F.R. § 314.50 (requiring "reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source"); *id*. § 314.50(d)(5)(vi)(a) (requiring "an integrated summary of all available information about the safety of the drug product, including pertinent animal data[and] demonstrated or potential adverse effects of the drug"); *id*. § 312.50 (stating that "[s]ponsors are responsible for . . . providing [investigators] with the information they need to conduct an investigation properly . . . and ensuring that [the] FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug"). The FDA approval process is "onerous and lengthy." *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013).

manufacturer, similarly, maintains "a duty to provide a warning that adequately describe[s] that risk," *Wyeth*, 555 U.S. at 571, and "bears responsibility for the content of its label at all times," *Merck*, 139 S.Ct. at 1677 (explaining that this has "remained a central premise of federal drug regulation"), regardless of whether the FDA takes parallel action.

C. *The Fosamax Label History*

When the FDA approved Fosamax in 1995, the label did not warn of a risk of the adverse event Plaintiffs allege here, *i.e.*, atypical femoral fractures. *Fosamax*, 852 F. 3d at 271, 274-75. However, Merck was "aware of at least a theoretical risk" of such particular fractures as early as 1992, during clinical trials, and brought it to the FDA's attention at that time. *Merck*, 139 S. Ct. at 1674 (informing the FDA that "antiresorptive agents may inhibit microdamage repair by preventing . . . bone resorption at the sites of microdamage"). More evidence came to light after 1995, when "Merck began receiving adverse event reports from the medical community indicating that long-term Fosamax users were suffering atypical femoral fractures."[4] *Merck*, 139 S.Ct. at 1674. Based on its own analysis of these increasing reports, in 2005, Merck preliminarily concluded that there was a statistically significant increase in the incidence of

[4] For example, in 2002, Merck received a report from a doctor who said that his hospital called atypical femoral fractures the "Fosamax Fracture" because "100% of patients in his practice who have experienced femoral fractures (without being hit by a taxicab), were taking Fosamax . . . for over 5 years." *Merck*, 139 S.Ct. at 1674 (quotations and citations omitted).

atypical femoral fractures among Fosamax users. Pl. Br., Ex. 8, at A1272-73.

Merck also "began to see numerous scholarly articles and case studies documenting possible connections between long-term Fosamax use and atypical femoral fractures." *Merck*, 139 S.Ct. at 1674. However, none of these studies concluded that Fosamax actually caused atypical femoral fractures, or even that they were definitively associated with Fosamax use. *Fosamax*, 852 F.3d at 275 (citing A1258) (stating that Fosamax may potentially increase the risk of such fractures); *id*. (citing A1237) (stating that Fosamax may be associated with such fractures; *id*. (citing A1243) (stating that certain findings raised the possibility that Fosamax may lead to such fractures). Still, Merck forwarded them to the FDA. *Fosamax*, 862 F.3d at 275.

In March 2008, Merck submitted to the FDA a 165-page periodic safety update, the twenty-ninth of its kind, with thirty pages dedicated to "recent publications" "implicat[ing] a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures," and "relat[ing] these findings to severely suppressed bone turnover that may develop during long-term" use of Fosamax. Def. Rep. Br., Ex. 14, at A2597. Later that month, Merck sent the FDA a letter from the New England Journal of Medicine describing "a potential link between [bisphosphonate] use and low-energy fractures of the femur." *Id*., Ex. 13. The FDA, in turn, informed Merck in June 2008, that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and was "concerned about this developing safety signal." Pl. Br., Ex. 10, at A1145.

The Agency asked Merck for additional data and investigations by July 2008, and Merck complied.

In September 2008, while its data was pending review, Merck submitted to the FDA a PAS, *i.e.*, application to enlarge the warning label, to amend the Adverse Reactions section of the Fosamax label with a warning about "low-energy femoral shaft fractures," *id.*, Ex. 38, at A1349, and to cross-reference a longer discussion in the Precautions section. *Merck*, 139 S.Ct. at 1674. Specifically, Merck proposed adding the following language to the Precautions section:

> ***Low-Energy Femoral Shaft Fracture***
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in

> patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pl. Br., Ex. 38 at A1371.[5]

As part of its PAS to the FDA, Merck submitted a lengthy analysis of femoral fractures in Fosamax users, cited to nine articles on such cases, and summarized the findings in a clinical overview. Merck opined that, although "[i]t is not possible with the present data to establish whether" Fosamax "increases the risk of . . . low-energy subtrochanteric and/or proximal shaft fractures," because they tended to arise alongside Fosamax use, it is "important to include an appropriate statement" about them in the drug's precautions section. *Id*., Ex. 38, at A1349-51.

In April 2009, Merck discussed its pending PAS with FDA official, Dr. Scott Monroe. According to Merck's notes, Dr. Monroe expressed that, while the FDA could agree to additional language in the Adverse Reactions section, it likely would not approve similar language in the Precautions section. Pl. Br., Ex. 33, at

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[5] Based on a review of scientific studies in the record, including the FDA's September 2010 Task Force Report, as mentioned *supra*, I note that "low-energy femoral shaft fractures" are the same as "atypical femoral fractures." *See* Pl. Br., Ex. 2, at A1152. In layman's terms, "atypical femoral fractures" are a "rare type of complete, low-energy fracture [that] affects the thigh bone." *Merck*, 139 S.Ct. 1674. The low-energy component, critical to both terms, generally means that the fracture was caused by a slip, trip, or fall from standing height or less. *See* Pl. Br., Ex. 2. At A1152. Thus, low-energy fractures are typically caused by mechanical forces that would not ordinarily result in fracture, while high-energy fractures, on the other hand, are generally associated with a more focused and substantial trauma.

A1970-71. Dr. Monroe advised that the FDA would likely "approach the issue of a precaution from the [perspective] of all bisphosphonates [from various drug manufacturers]" and was "working with the Office of Safety and Epidemiology ["OSE"] to do so." *Id.* But, because "the conflicting nature of the literature does not provide a clear path forward, . . . more time will be need[ed] for FDA to formulate a formal opinion on the issue of a precaution." *Id.* In Dr. Monroe's view, Merck's "elevation" of the warning to a Precaution was "prolonging" approval of any amendment to the label. *Id.*

Later that month, an FDA official emailed Merck that the FDA was not prepared to include language about low-energy femoral fractures in the Precautions section, and "could . . . only" "approve[]" such a warning "in the adverse events section of the label." Def. Br., Ex. 3, at A1498. The official asked Merck to "hold off on the [Precautions] language" so that drug evaluators could "work with [the Office of Surveillance and Epidemiology] and Merck to decide on . . . atypical fracture language, if it is warranted." *Id.* The next month, in May 2009, officially responding to Merck's PAS, Dr. Monroe drafted a CRL which stated that the FDA approved a warning in the Adverse Reactions section, subject to some rewording, but rejected one in the Precautions section. Then, the FDA explained:

> We have completed the review of your [PAS], as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.

> 1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS**, **Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

Def. Br., Ex. 2, at A1500-01.

On the same day that the FDA sent the CRL, Merck "asked the [Agency]" for a "teleconference to discuss what [Precautions language] may be acceptable." Pl. Br., Ex. 13. A few weeks later, undeterred, Merck again asked "for a meeting . . . to discuss the issues that were raised in the [CRL] to Merck's proposed text to the Precautions section." *Id.*, Ex. 14. Merck also asked to "leave the previous PAS active to permit further discussions with the agency." *Id.*, Ex. 15. The FDA "informed [Merck] that the proposal was not in-line with Dr. Monroe's request that all deficiencies need to be addressed to start a new review cycle," and any meeting must be formally requested. *Id.* Merck maintained that "[atypical] fractures should [still] be described in the Precautions section," and suggested "broach[ing]" that topic in an unrelated teleconference the following day, to which the FDA responded it might be "possible," albeit "not the objective of the meeting." *Id.*

Pursuant to FDA regulations, within one year of the CRL, Merck had to "resubmit" its application "addressing all deficiencies identified" in the CRL, withdraw it, or request a hearing, after which "the agency will either approve" or "refuse" the label change. 21 C.F.R. § 314.110(b). In July 2009, Merck elected to withdraw, Def. Br., Ex. 4, at A2961, change the Adverse Reactions section through a CBE amendment, as recommended by the FDA, *id*. at A2963-64, and leave the Precautions section as-is. But, Merck did not do so without reiterating, once more, its desire to add a Precautions warning. *Id*.

Unwavering, in March 2010, after reviewing the data submitted by Merck (and other manufacturers), the FDA issued a Drug Safety Announcement reiterating that there was not yet "a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Def. Br., Ex. 5, at A1508-09. The FDA, however, announced that it would work with an outside Task Force, which included various experts in different agencies, to gather additional information. *Id*. In September 2010, the Task Force found that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture," although not enough to establish causation. Pl. Br., Ex. 2, at A1167. The FDA responded with another Drug Safety Announcement stating that, "[a]lthough it is not clear if bisphosphonates are the cause [of fractures], these unusual femur fractures have been identified in patients taking [such] drugs." Def. Br., Ex. 9, at A1512. The FDA then "assembled and [reviewed] all long term data available on the products, as well as all

safety reports," and promised to "keep the public informed of additional findings." *Id*.

In October 2010, more than a year after the FDA sent Merck its CRL, the FDA, after completing its analysis, finally concluded that "atypical fractures may be related to long-term . . . bisphosphonate use," and announced that it would require all bisphosphonate manufacturers to add information on that risk to the Precautions sections of their labels. Pl. Br., Ex. 19, at A1118. In a media call accompanying the announcement, the FDA's Deputy Director of the Office of New Drugs stated that the Task Force Report made the Agency "confident" that atypical femur fractures are "potentially more closely related to" long-term use of bisphosphonates "than [we] previously had evidence for." Def. Br., Ex. 6, at A1396. The FDA wrote to Merck that day to mandate a label change to Fosamax. Def. Br., Ex. 7, at A1516-17. Specifically, the FDA provided language for a warning in the Precautions section:

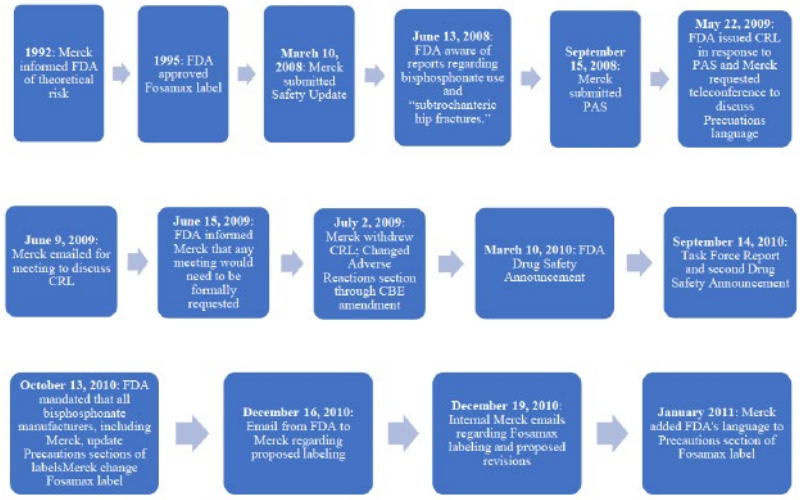
> ***Atypical Subtrochanteric and Diaphyseal Femoral Fractures*:**
>
> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

> Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
>
> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Id.

In response, Defendant proposed revised language that, once again, referred to the risk of "stress fractures." Pl. Br., Ex. 21, at A1556-57. But, the FDA rejected that language, explaining that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." *Id.* at A1540. In January 2011, Merck added the FDA's language, nearly verbatim, to the Precautions section of the Fosamax label. *Id.*, Ex. 1, at A1070-71. That warning remains in place today.

Before discussing the case's procedural history, it is helpful to summarize the timeline of events:



D. *The Parties Prior Litigation*

After the label change, Plaintiffs filed separate actions, in different states, seeking tort damages under state law. They claimed that, during the relevant period, Merck had a legal duty to warn them about the risk of atypical femoral fractures. Merck argued, in response, that federal law preempted Plaintiffs' claims—specifically, the May 2009 CRL rejecting Merck's proposed label change.[6]

Following a bellwether trial, Judge Pisano agreed with Merck, and granted summary judgment in all cases. *OTSC Opinion*, 2014 WL 1266994, at *17

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[6] In 2011, the Judicial Panel on Multidistrict Litigation consolidated these cases, which once exceeded 1,000 cases, for pre-trial administration in a multi-district litigation ("MDL") in the District of New Jersey. *In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F. Supp. 2d 1355 (J.P.M.L. 2011).

(D.N.J. Mar. 22, 2014); *Glynn*, 951 F. Supp. 3d at 701, 703-04. In particular, Judge Pisano found, "the fact that the FDA never required [Merck] to submit new language or change the label [after rejecting its proposed warning] demonstrates that the FDA did not think that the label should have been changed at that time," and there was "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning." *OTSC Opinion*, 2014 WL 1266994, at *16 (emphasis in original). Indeed, Judge Pisano explained that pursuant to the Supreme Court's decision in *Wyeth*, a state law failure-to-warn claim is preempted if there is "clear evidence" that the FDA "would not have approved" any and all warnings.

Plaintiffs appealed the decision to the Third Circuit, which vacated Judge Pisano's decision. *Fosamax*, 852 F.3d 268. While recognizing that *Wyeth* controls the analysis, the Court of Appeals reasoned that "[t]he term 'clear evidence' . . . does not refer directly to the *type* of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate." *Id*. at 285. "Rather, it specifies how *difficult* it will be for the manufacturer to convince the factfinder that the FDA would have rejected a proposed label change." *Id*. And, the court determined that the factfinder must be a jury not a judge. In that regard, the circuit court devised a novel standard: "for a defendant to establish a preemption defense under *Wyeth*, the [jury] must conclude that it is highly probable that the FDA would not have approved a change to the drug's label." *Id*. at 286.

Accepting Merck's petition for certiorari, the Supreme Court vacated the Third Circuit's opinion

and judgment, holding that preemption must be decided by "a judge, not the jury," who, in turn, "must simply ask himself or herself whether the relevant federal and state laws irreconcilably conflict." *Merck*, 139 S.Ct. at 1676, 1679-80 (quotations and citation omitted). The Court also "elaborate[d] *Wyeth*'s" clear evidence standard "along the way." *Id*. It explained that "[c]lear evidence" exists where a drug manufacturer "show[s] that it 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 changing the drug's label to include that warning." *Id*. at 1678. This will not "ordinarily" be the case. *Id*. at 1679. Moreover, "whatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated," an "obvious point" which the Court reiterated even though "[t]he question of disapproval method is not now before [the Court]."[7] *Id*. at 1679-80.

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[7] Justice Thomas wrote separately to explain his "understanding of the relevant pre-emption principles and how they apply to this case." *Merck*, 139 S.Ct. at 1681 (Thomas, J., concurring). Justice Thomas would not find preemption here because, in his view, nothing prevented Merck from using the CBE process to unilaterally add a warning to the Precautions section, even though the FDA retains the authority to reject a CBE amendment if it lacks causation. *Id*. at 1683. Further, according to Justice Thomas, even if Merck believed that the FDA would have ultimately rejected a CBE amendment, that "hypothetical" would not constitute "[l]aw with pre-emptive effect," because "the possibility of impossibility is not enough." *Id*. Justice Thomas also rejected the preemptive effect of a CRL to the extent that such a letter is not a final agency action. *Id*. at 1682. In response, Justice Alito wrote separately to ensure that the Court's

The Supreme Court remanded to the Third Circuit with instructions "to consider fully the standards we have described." *Id.* at 1680-81. Rather than deciding the issue, the Third Circuit remanded to this Court "to determine in the first instance whether the plaintiffs' state law claims are preempted by federal law." Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019). The Third Circuit also instructed this Court "to determine the effect of the FDA's [CRL] and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." *Id.*

E. *The Parties' Arguments on Remand*

The issue on remand is the same as it was eight years ago: whether the CRL "prohibited [Merck] from adding any and all warnings to the drug label that would satisfy state law." *Merck*, 139 S.Ct. at 1678. Plaintiffs answer in the negative, and advance several arguments, some of which merely restate their prior positions. First, they reiterate that Merck did not fully

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"discussion of the law and the facts" are not "misleading on remand." *Id.* at 1684 (Alito, J., concurring in the judgment). Chief Justice Roberts and Justice Kavanaugh joined his opinion. Justice Alito explained that "a statutory provision enacted after the events in [*Wyeth*] [ ] may have an important bearing" on this case, namely 21 U.S.C. § 355(o)(4)(A), which requires the FDA to initiate a label change under certain circumstances, but does not require it "to communicate to the relevant drug manufacturer that a label change is unwarranted; instead, the FDA could simply consider the new information and decide not to act." *Id.* Justice Alito then detailed the back and forth between Merck and the FDA to counter the majority's "one-sided account," stating "for years the FDA was: aware of this issue, communicating with drug manufacturers, studying all relevant information, and instructing healthcare professionals and patients alike to continue to use Fosamax as directed." *Id.* at 1685-86.

inform the FDA of the risks of Fosamax use. Pl. Br., at 30-35. Second, relying on Justice Thomas' concurrence, they argue for the first time during this litigation that the CRL does not carry preemptive effect because it is not a final agency action, *id*. at 12-15, 27; however, they primarily dispute the meaning and scope of the CRL. They begin by arguing that Merck did not propose a warning that would have been adequate under state law in the first place. According to Plaintiffs, Merck's PAS emphasized "garden variety" stress fractures, which are scientifically different from the more serious atypical femoral fractures. *Id*. at 16-19, 24 n.4. Because of this focus, Plaintiffs posit that the FDA could not have rejected a warning about atypical femoral fractures at all, but only one about commonplace stress fractures. So construed, Plaintiffs advance that the CRL does not constitute "clear evidence" that the FDA would have prohibited any and all warnings to Fosamax, despite the Agency's other communications from the same time period. *Id*. at 24-30.

Merck maintains that it has always fully informed the FDA of the risks of Fosamax, particularly the risk of developing atypical femoral fractures. Def. Br., at 17-20; Def. Rep. Br., at 1-4. Merck also calls Plaintiffs' position that the CRL lacks preemptive power "idiosyncratic" and "unsupported" by law. Def. Br., at 28-30; Def. Rep. Br., at 11-12. Further, as to the meaning and scope of the CRL, Merck argues that its proposed warning was "perfectly" adequate under state law, *see* Def. Br., at 5-6, 14, 20-24, and the FDA rejected it for insufficient causal evidence linking bisphosphonate use to atypical femoral fractures, not because of the garden variety "stress fracture"

language on which Plaintiffs improperly focus. Def. Br., at 23-27; Def. Rep. Br., at 10-11. As explained by Merck, to the extent that the basis for the CRL was the FDA's skepticism of the underlying science regarding causal connection, there is necessarily clear evidence that the FDA would have rejected any and all changes to the Fosamax label. *See* 21 C.F.R. § 201.57(c)(6)(iii) (requiring "reasonable evidence of a causal association" to add a Precautions warning). Finally, even if the terms of the CRL themselves are unclear, Merck maintains that the letter constitutes clear evidence when construed in light of the FDA's other communications from around the same time. Def. Br., at 8-9, 21-23, 26; Def. Rep. Br., at 12-13, 15.

In short, Merck submits that the CRL conveyed that the FDA would not have approved any warning about atypical femoral fractures because of its then-existing perspective on the causal connection between such fractures and Fosamax use. Plaintiffs, on the other hand, take the position that the FDA had conveyed a far more limited message in the CRL: Merck's particular warning, as worded, was unacceptable, but the FDA might have approved different language had Merck proposed it through a revised PAS or a CBE amendment.

STANDARD OF REVIEW[8]

Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and

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[8] While the parties' briefing does not discuss the legal standard the Court should apply on remand, they agreed that Rule 56 was the proper framework by which Judge Pisano resolved the dispositive issues presented by Defendant's preemption defense in the first instance. *Fosamax*, 852 F.3d at 281 ("Although both

admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). A factual dispute is genuine only if there is "a sufficient evidentiary basis on which a reasonable [factfinder] could find for the non-moving party," and it is material only if it has the ability to "affect the outcome of the suit under governing law." *Kaucher v. Cty. of Bucks*, 455 F.3d 418, 423 (3d Cir. 2006); *see also Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). Disputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment. *Anderson*, 477 U.S. at 248. "In considering a motion for summary judgment, a district court may not make credibility determinations or engage in any weighing of the evidence; instead, the non-moving party's evidence 'is to be believed and all justifiable inferences are to be drawn in his favor.'" *Marino v. Indus. Crating Co.*, 358 F.3d 241, 247 (3d Cir. 2004) (quoting *Anderson*, 477 U.S. at 255); *see also Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986); *Curley v. Klem*, 298 F.3d 271, 276-77 (3d Cir. 2002).

The party moving for summary judgment has the initial burden of showing the basis for its motion. *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986). "If

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sides disputed the propriety of the show-cause procedure and the substance of Merck's preemption arguments, the parties and the District Court all agreed that Federal Rule of Civil Procedure 56 'provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s).'"). Accordingly, because the Third Circuit remanded that very issue to me, I will apply that same standard, here.

the moving party will bear the burden of persuasion at trial, that party must support its motion with credible evidence ... that would entitle it to a directed verdict if not controverted at trial." *Id.* at 331. On the other hand, if the burden of persuasion at trial would be on the nonmoving party, the party moving for summary judgment may satisfy Rule 56's burden of production by either (1) "submit[ting] affirmative evidence that negates an essential element of the nonmoving party's claim" or (2) demonstrating "that the nonmoving party's evidence is insufficient to establish an essential element of the nonmoving party's claim." *Id.* Once the movant adequately supports its motion pursuant to Rule 56(c), the burden shifts to the nonmoving party to "go beyond the pleadings and by her own affidavits, or by the depositions, answers to interrogatories, and admissions on file, designate specific facts showing that there is a genuine issue for trial." *Id.* at 324; *see also Matsushita*, 475 U.S. at 586; *Ridgewood Bd. of Ed. v. Stokley*, 172 F.3d 238, 252 (3d Cir. 1999). In deciding the merits of a party's motion for summary judgment, the court's role is not to evaluate the evidence and decide the truth of the matter, but to determine whether there is a genuine issue for trial. *Anderson*, 477 U.S. at 249. Credibility determinations are the province of the factfinder. *Big Apple BMW, Inc. v. BMW of N. Am., Inc.*, 974 F.2d 1358, 1363 (3d Cir. 1992). There can be "no genuine issue as to any material fact," however, if a party fails "to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex*, 477 U.S. at 322-23. "[A] complete failure of proof concerning an essential element of the

nonmoving party's case necessarily renders all other facts immaterial." *Id.* at 323; *Katz v. Aetna Cas. & Sur. Co.*, 972 F.2d 53, 55 (3d Cir. 1992).

DISCUSSION

I. *Scope of Remand*

The Third Circuit's mandate to this Court is clear: to determine whether Plaintiffs' state law failure-to-warn claims are preempted by federal law under the standards described by the Supreme Court in *Merck*. Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019). In considering that question, the Third Circuit also instructed this Court to determine whether the FDA's CRL and other communications with Defendant are sufficient to give rise to preemption. *Id.*

As a preliminary matter, I note that on appeal, the Third Circuit vacated in full, Judge Pisano's underlying decision granting summary judgment in favor of Defendant, and the Supreme Court remanded with instructions to "consider fully" its elaboration of *Wyeth*'s clear evidence standard. Although I will conduct a *de novo* review of the legal issues and record, that does not necessarily mean, however, that Judge Pisano's factual findings will be ignored. In fact, my decision, here, will refer to Judge Pisano's opinion—at least as it relates to certain facts that are generally not in dispute. Indeed, Judge Pisano held a full trial on the merits, heard expert testimony, made numerous factual findings related to the narrow legal question on appeal in *Merck*, decided the preemption inquiry, and unsurprisingly, the evidence before me is virtually identical to the evidence presented then. To be certain, in 2013, Judge Pisano answered the preemption question posed to the Court on remand,

here, consistent with the standard set forth in *Wyeth*—a standard that the Supreme Court did not overrule, but merely clarified and expounded upon in *Merck*. *See infra*. Indeed, *Merck* decided the narrow question of whether a jury or judge determines preemption—agreeing with Judge Pisano that it was a question for a judge. That issue constitutes new law, which I take as the law of this case now. *Bankers Trust Co. v. Bethlehem Steel Corp.*, 761 F.2d 943, 950 (3d Cir. 1985). But, what remains is exactly what Judge Pisano had to decide eight years ago: assess "in the first instance" whether "the FDA would have rejected a change," considering any relevant factual disputes along the way. For these reasons, I will refer to Judge Pisano's factual findings where appropriate.

II. *Preemption*

"A fundamental principle of the Constitution is that Congress has the power to preempt state law." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000). "Preemption follows automatically by the operation of the Supremacy Clause," *Wyeth*, 555 U.S. at 624 (Alito, J., concurring in the judgment), which "invalidates state laws that interfere with, or are contrary to, federal law." *Hillsborough County, Florida v. Automated Medical Laboratories, Inc.*, 471 U.S. 707, 712 (1985) (quotations omitted). Federal law can preempt state law in three ways: (1) express preemption, (2) field preemption, and (3) conflict preemption.[9] *Farina v. Nokia Inc.*, 625 F.3d 97, 115

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[9] Federal regulations with the force of law preempt state laws in the same manner as federal statutes. *See, e.g., Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000); *Fellner v. Tri-Union Seafoods, L.L.C.*, 539 F.3d 237, 243 (3d Cir. 2008) ("Where

(3d Cir. 2010). Both parties agree that the issue in this case is conflict preemption, which exists "where it is impossible for a private party to comply with both state and federal requirements." *Sprietsma v. Mercury Marine, a Div. of Brunswick Corp.*, 537 U.S. 51, 64 (2002) (quotations omitted); *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011) ("The question . . . is whether the private party could independently do under federal law what state law requires of it."); *Klotz v. Celentano Stadtmauer & Walentowicz LLP*, 991 F.3d 458, 463 (3d Cir. 2021).

Conflict, or impossibility, preemption "is a demanding defense" in the drug labeling context. *Wyeth*, 555 U.S. at 573. Essentially, a defendant must show that it could not have unilaterally changed its label in any way to add the warning required by state law. *Id.* at 569-71; *Sikkelee v. Precision Airmotive Corp.*, 822 F.3d 680, 703-704 (3d Cir. 2016); *Knight v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 984 F.3d 329, 337 (4th Cir. 2021) ("A state law challenge to FDA-approved warnings, including a tort action under state law, can [ ] proceed only when the defendant had the unilateral ability to change that labeling; otherwise, the claim is preempted.").

Congress has delegated the authority to regulate a particular field to an administrative agency, the agency's regulations issued pursuant to that authority have no less preemptive effect than federal statutes, assuming those regulations are a valid exercise of the agency's delegated authority."). There is no dispute here that preemption, if appropriate, applies to all forms of state law, including civil actions based on state law, such as Plaintiffs' failure-to-warn claims. *Holk v. Snapple Beverage Corp.*, 575 F.3d 329, 331 (3d Cir. 2009).

The "possibility of impossibility [is] not enough" to establish preemption, *PLIVA*, 564 U.S. at 624 n.8 (quotations omitted); *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982) (rejecting "hypothetical" impossibility), and there is a "presumption against preemption," *Wyeth*, 555 U.S. at 595 n.3, which applies with special force in fields involving traditional state police powers. *Medtronic, Inc., v. Lohr*, 518 U.S. 470, 485 (1996) ("In all pre-emption cases, and particularly in those in which Congress has 'legislated . . . in a field which the States have traditionally occupied,' . . . [courts] 'start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'"). On the other hand, "the possibility of possibility" is not sufficient to *defeat* preemption. *PLIVA*, 564 U.S. at 624 n.8.

Rather, under *Wyeth*, if there is "clear evidence that the FDA would not have approved a change" to a drug's label, then it is impossible to comply with both federal and state law, and a plaintiff's failure-to-warn claims are preempted. 555 U.S. at 571. To establish clear evidence, a drug manufacturer must "show that it 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 changing the drug's label to include that warning." *Merck*, 139 S.Ct. at 1678.

A. *Merck* Did Not Repudiate *Wyeth*[10]

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[10] In *Wyeth*, the Supreme Court rejected a drug manufacturer's preemption defense after an antinausea drug caused a patient to develop gangrene. Notably, there was no prior agency action in that case. The question was whether the FDA would have

At the outset, Plaintiffs contend that *Merck* repudiates *Wyeth*'s "premise that a manufacturer can show preemption by arguing that the FDA *would have* rejected a warning that it did not actually reject." Pl. Br., at 13-14 (emphasis in original). In Plaintiffs' view, impossibility preemption now "requires an affirmative showing that the FDA took 'action[]' to 'prohibit[] the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law.'" Pl. Br., at 14 (quoting *Merck*, 139 S.Ct. at 1676, 1678).

Plaintiffs' position has some facial appeal, but it is ultimately specious. In *Wyeth*, the phrase "would not have approved" implies that a drug manufacturer may prove preemption without showing that it ever proposed or pursued a label change. Plaintiffs argue, however, that *Merck*'s phrasing of the law should be read to mean that a manufacturer must have *actually requested* a label change that the FDA *then expressly rejected*.[11] Specifically, Plaintiffs rely exclusively on the Supreme Court's finding that to establish preemption, a manufacturer "is required to show that it fully informed the FDA of the justifications for the

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rejected a CBE amendment had the manufacturer attempted to pursue one. However, *Wyeth* does not instruct how this Court should interpret the meaning of an actual FDA decision on labeling, such as the CRL here that rejected Merck's proposed warning, which is the crux of this case.

[11] Of course, this is precisely the factual scenario of this case; that is, Defendant claims that the CRL issued by the FDA expressly rejected Defendant's proposed warning regarding atypical femoral fractures. And, the primary dispute between the parties is whether the CRL could be so interpreted as to have rejected Defendant's proposed warning based on the causal connection between the use of Fosamax and atypical femoral fractures.

warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Merck*, 139 S.Ct. at 1678. According to Plaintiffs, "anything less is insufficient." Pl. Br., at 14.

The Seventh Circuit has declined to view *Merck* in that manner, and I find that court's reasoning persuasive. *Dolin v. GlaxoSmithKline*, 951 F.3d 882, 890-91 (7th Cir. 2020). Indeed, the court, there, observed, in the context of a Rule 60(b) motion, that *Merck* "explicitly grounded its analysis in the Court's holdings in *Wyeth* . . . . began by citing the *Wyeth* 'clear evidence' standard[,] and formulated the question for decision in terms of the *Wyeth* framework," and further, that *Merck* uses "the language of ordinary evolution" rather than 'reversal and overruling." The Tenth Circuit ruled similarly. *Cerveny v. Aventis, Inc.*, 783 Fed. App'x. 804 n.8 (10th Cir. 2019) (dismissing, in the context of a Rule 28(j) letter, the contention that "only labeling changes sought by the manufacturer can lead to preemption.")

The Third Circuit also had an opportunity to reinterpret *Wyeth* in the manner proposed by Plaintiffs, but chose not do so in light of the facts before it. *In re Avandia Marketing, Sales and Prod. Liab. Litig.*, 945 F.3d 749, 759 (3d Cir. 2019) (stating that it "need not speculate regarding the possibility that the FDA would have rejected the proposed warning" because the FDA in fact "*ordered*" one) (emphasis in original). In dozens of district court cases since, not one court has interpreted *Merck* to establish a new standard for impossibility preemption requiring actual agency or manufacturer action. *See, e.g., In re Incretin-Based Therapies Prod. Liab. Litig.*, No. 13-

2452, 2021 WL 880316 (S.D. Cal. Mar. 9, 2021) ("Plaintiffs also contend that [*Merck*] limited preemption to cases where the manufacturer has proposed a label change. The Court, however, does not read [*Merck*] so narrowly. Rather, the Court finds that [*Merck*] simply reiterated the lesson in *Wyeth* that the availability of the CBE label change process makes it such that a manufacturer will not 'ordinarily' be able to show an irreconcilable conflict between state and federal law."); *Crockett v. Luitpold Pharmaceuticals, Inc.*, No. 19-276, 2020 WL 433367, at *6 (E.D. Pa. Jan. 28, 2020) ("The defense of impossibility preemption is premised on a contention that a federal regulation would have prohibited the additional warnings that the plaintiff alleges state law requires."); *Yamagata v. Reckitt Benckiser LLC*, 445 F. Supp. 3d 28, 33 (N.D. Cal. 2020) ("The preemption analysis in [*Merck*] turned on whether the FDA would have approved a change to the drug label."); *McGrath v. Bayer HealthCare Pharmaceuticals, Inc.*, 393 F. Supp. 3d 161, 171 (E.D.N.Y. 2019) (finding preemption because the plaintiff "has not pleaded a plausible claim that the CBE regulation would have permitted [the defendant] to change the [drug] label"); *Silverstein v. Boehringer Ingelheim Pharmaceuticals, Inc.*, No. 19-81188, 2020 WL 6110909, at *9 (S.D. Fla. Oct. 7, 2020) ("[Preemption] can be satisfied [under *Merck*] even if the labeling change has not been presented to, and rejected by, the FDA.").

As such, based on these authorities, 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*. *See, e.g., Cerveny v. Aventis, Inc.*, 155 F. Supp. 3d 1203, 1213-16 (D.

Utah Mar. 16, 2016) ("Courts have universally rejected the notion that *Wyeth* requires a showing that the manufacturer attempted to apply the warning suggested by the plaintiff but that the labeling change was ultimately rejected by the FDA."); *In re Zofran (Ondansetron) Prod. Liab. Litig.*, No. 15-2657, 2021 WL 2209871, at *32 (D. Mass. June 1, 2021) ("Multiple courts have found [conflict] preemption where the manufacturer had not requested the precise warning sought by the plaintiffs when the FDA had nonetheless made it clear that it would not accept that label change."); *Ridings v. Maurice*, 444 F. Supp. 3d 973, 998 (W.D. Mo. 2020) (finding the second prong of *Merck* to be satisfied when all of the information justifying the proposed warning had been given to the FDA and the FDA did not revise the label to add the warning); *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1170 (S.D. Cal. May 11, 2016) ("[M]anufacturer submission of a proposed labeling change is relevant, but not dispositive, in determining whether a defendant can establish conflict preemption.").

In the end, it is, of course, the Supreme Court's "prerogative alone to overrule one of its precedents." *State Oil v. Khan*, 522 U.S. 3, 20 (1997). But it is difficult to reconcile the Court doing so when no party disputed *Wyeth*'s clear evidence standard on appeal,[12] when the question before the Court was who should apply that standard, not whether the standard should survive, and when the Court itself held that its decision "flow[ed] *from* [its] precedents." 139 S.Ct. at

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[12] Tellingly, Plaintiffs themselves argued on appeal that *Wyeth* "was correctly decided." U.S. Merits Brief, at *25-28.

1678 (emphasis added). Accordingly, like all other courts having considered the issue, I find that *Merck* does not overrule *Wyeth*.

B. *Prong One of Impossibility Preemption*

I now turn to the substance of the parties' dispute. To establish impossibility preemption, a drug manufacturer must first show that it "fully informed the FDA of the justifications for the warning required by state law." *Merck*, 139 S.Ct. at 1678. I find that Defendant has met this standard; indeed, Judge Pisano found as much, the Third Circuit agreed, and the Supreme Court never questioned that finding on appeal. I reach the same conclusion based on my independent evaluation of the record.

After a full trial on the merits, including extensive expert testimony, Judge Pisano found no evidence that "Defendant failed to provide all the information it had . . . to the FDA." *Glynn*, 951 F. Supp. 2d at 703, 705. After a post-trial opportunity for Plaintiffs to present further proof, Judge Pisano again rejected their claim as "speculation." *OTSC Opinion*, 2014 WL 1266994, at *14, *17. The Third Circuit characterized the record in more certain terms: "Merck kept the FDA informed of the scores of case studies, reports, and articles . . . published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures," and "[i]t is undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010." *Fosamax*, 852 F.3d at 275, 296. The Supreme Court did not consider—let alone challenge—these factual findings on appeal. *Merck*, 139 S.Ct. at 1680.

Plaintiffs disagree, pointing first to the way in which the Supreme Court's summary of the facts characterizes what the FDA knew and when.[13] *See, e.g., Merck*, 139 S.Ct. at 1673-76. But that is insufficient to support the inference that the Court *actually found* that Merck did not fully inform the FDA of the risks of Fosamax. For one, the Court is "an appellate tribunal, ill-equipped for the task of factfinding," and prong one of impossibility preemption is a fact-intensive inquiry involving a record exceeding one-thousand pages. *Ohio v. Wyandotte Chems. Corp.*, 401 U.S. 493, 498 (1971). More to the point, the Court does not "lightly overturn the concurrent findings of the two lower courts" on

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[13] Generally speaking, the Supreme Court used a harsher tone when describing Merck's actions throughout the labeling process. *Merck*, 139 S.Ct. at 1673-76. The Court stated that at the time the FDA first approved the Fosamax label in 1995, Merck scientists were aware of the risk of atypical femoral fractures, but "perhaps because [Merck's] concerns were only *theoretical*, the FDA approved Fosamax's label without requiring any mention of this risk." *Id.* at 1674 (emphasis added). Then, in 2008, after additional scientific evidence arose connecting Fosamax to atypical femoral fractures, the Court explained that Merck applied to the FDA for preapproval to change the drug's label, attempting to add language to both the Adverse Reactions and the Precautions sections of the label. *Id.* The Court emphasized that although the FDA denied Merck's request, it also invited the manufacturer to "resubmit" its application to "fully address all the deficiencies" identified by the FDA's review. *Id.* According to the Court, however, Merck "instead withdrew its application," choosing to make the changes to the Adverse Reactions section through the CBE process. *Id.* Moreover, with respect to the Fosamax label's eventual warning about atypical femoral fractures, the Court commented that Merck was "initially resistant" to the change, because it failed to reference "stress fractures." *Id.* at 1674-75.

factual matters, in the background section of an opinion, especially not without any explanation, and when such findings were never on review in the first place. *Glossip v. Gross*, 576 U.S. 863, 882 (2015); *Exxon Co., U.S.A. v. Sofec, Inc.*, 517 U.S. 830, 841 (1996) (explaining that the Court "'cannot undertake to review concurrent findings of fact by two courts below in the absence of a very obvious and exceptional showing of error'") (quoting *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 336 U.S. 271, 275 (1949)); *cf. Easley v. Cromartie*, 532 U.S. 234, 242 (2001) (doing so only when "there is no intermediate court," "we are the only court of review," "the trial here at issue was not lengthy and the key evidence consisted primarily of documents and expert testimony," and "[c]redibility evaluations played a minor role"). Saliently, Justice Alito concurred in part to ensure that the majority's "discussion . . . of the facts is not misleading." *Merck*, 139 S.Ct. at 1684. On this point, Justice Alito wrote, "[r]esolution of the legal question that the Court decides does not require much discussion of the facts, but . . . . the Court provides a one-sided account . . . [that] omits any mention of the extensive communication between Merck and the FDA during the relevant period." *Id.* at 1685. In the end, Plaintiffs' position cannot be reconciled with the Court's explicit decision to remand with instructions to apply its standards anew. *Cf. Farrar v. Hobby*, 506 U.S. 103 (1992) (deciding the merits rather than remanding); *McCkeskey v. Zant*, 499 U.S. 467 (1991) (same).

Plaintiffs then argue that the standard Judge Pisano applied in *Glynn* is somehow less demanding than *Merck*'s requirement that Defendant "fully"

inform the FDA. Pl. Br., at 32-34 ("Judge Pisano did not apply the Supreme Court's standard [in *Merck*]."). But Plaintiffs never explain Judge Pisano's supposedly erroneous standard, the relevant difference between that standard and the *Merck* standard, or why such a difference would be legally significant. Independently, I do not see any meaningful difference between what *Merck* demands and what Judge Pisano determined. Under *Merck*, the basic inquiry, which Judge Pisano applied, is whether the FDA had "all the information it deemed necessary to decide whether to approve or reject the proposed warning at the time it issued the [CRL]." *In re Avandia*, 945 F.3d at 759 (emphasis removed). Indeed, *Merck* itself phrases the inquiry in a substantially similar way: "the litigants may dispute whether the drug manufacturer submitted all material information to the FDA." 139 S.Ct. at 1680.

In any event, revisiting this question as a matter of first impression, as instructed by the Third Circuit, I reach the same result as Judge Pisano. Between its formal safety updates, periodic emails, and PAS, Defendant clearly and fully informed the FDA of the panoply of risks associated with long-term Fosamax use and the justifications for its proposed label change. Having culled through the extensive record, I summarize below what Defendant submitted to the FDA. Defendant repeatedly and voluntarily sent relevant articles to the FDA between 1992 and 2010. *See Fosamax*, 852 F.3d at 275 (citing A1774, A1258, A1237, A1243); Def. Rep. Br., Ex. 13, at A1928-33; *Fosamax*, 862 F.3d at 275 (further describing communications). Indeed, Defendant's 165-page March 2008 safety update, which surveyed medical

studies, journal publications, and internal data compiled between July 16, 2007 and January 15, 2008, included numerous pages on atypical femoral fractures. Def. Rep. Br., Ex. 14. That safety update provided (1) an overview of three published safety studies identified in the medical literature describing new information regarding the connection between prolonged alendronate[14] use and low-energy or atypical femoral fractures, (2) a discussion of eight publications on long-term therapy with bisphosphonates, including the link between prolonged bisphosphonate therapy and atypical low-energy femoral fractures, and (3) a summary of post-marketing data on atypical low-energy fractures associated with prolonged bisphosphonate therapy in response to the FDA's request for such an update. *Id*. at A2594-2613.

With respect to the three safety studies and various publications, Merck cautioned that although they contain important clinical information, some of the studies and publications found no "obvious defects in mineralization or bone quality after use of the drug." *Id*. at A2595. However, Merck did highlight one particular study that "raised the possibility of a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures, predominantly with femoral diaphyseal location." *Id*. The authors of that study attributed this pattern of fractures to severely suppressed bone turnover that may develop during long-term alendronate therapy. *Id*. Similarly, several of the publications referenced in the safety update also hypothesized about a link

[14] Alendronate is a type of bisphosphonate.

between prolonged bisphosphonate therapy and the atypical low-energy fractures suffered by Plaintiffs. *Id*. at A2597-98. Finally, the safety update provided a trove of data, compiled from Merck's Worldwide Adverse Experience System database using search terms like "bone disorder," "stress fracture," "femur fracture," and "bone formation decreased." *Id*. at A2598-2613. Using these terms, Merck generated 175 post-marketing reports, providing insight into patients treated with alendronate sodium from October 1, 2005 through December 31, 2007. *Id*. at A2599. Specifically, the data from the post-marketing reports included, *inter alia*, the age and gender of the patient, location of the fracture, and the duration of alendronate therapy. *Id*. at A2609-10. While Merck commented that a review of the post-marketing reports did not provide "clear evidence of a causal link" between alendronate therapy and atypical low-energy femoral fractures, it committed to further monitor future reports for these types of fractures. *Id*. at A2613.

In June 2008, Defendant "promptly complied" with the FDA's request for further investigations that Merck had conducted and reports Merck had received. *Fosamax*, 862 F.3d at 275. And, what is more, Defendant's September 2008 PAS not only cited nine articles reporting cases of low-energy femoral fractures in Fosamax users, but included a clinical overview in which Defendant itself asserted a statistically significant association. *Cf. Wyeth*, 555 U.S. at 272-73 (noting that the manufacturer never "supplied the FDA with an evaluation or analysis concerning the specific dangers" at issue); *In re Taxotere (Docetaxel) Prod. Liab. Litig.*, No. 16-17039,

2020 WL 7480623, at *11 (E.D. La. Dec. 18, 2020) (finding that the FDA was not "fully informed" because its limited knowledge of the risk and repeated requests to the manufacturer for information indicated that the manufacturer was not "making an 'earnest attempt' to keep the FDA informed") (citations omitted). Despite this profuse evidence of information sent to the FDA, Plaintiffs, on remand, insist that more evidence was needed, and that Merck misled the FDA with the information it sent. Having reviewed, myself, those documents, I find no basis in the record to reach that conclusion.

In that regard, Plaintiffs' evidence that the FDA was somehow left in the dark about the use of Fosamax and the potential risk of atypical femoral fractures is unpersuasive. Plaintiffs begin by offering six specific studies between 1995 and 2010 which purport to show a connection between long-term bisphosphonate use and atypical femoral fractures. The flagrant flaw with Plaintiffs' proffer, however, is that Defendant cited all these same studies in its communications with the FDA. Plaintiffs then take issue with minute details of the data Defendant submitted to the FDA, which they insist shows that Defendant "provid[ed] misleading information . . . [,] describ[ed] atypical femoral fractures inaccurately and conflat[ed] them with stress fractures." Pl. Br., at 31-32. Specifically, Plaintiffs maintain that Defendant (1) did not "provide the FDA with any possible pathogenesis for [atypical femoral fractures]," *id*., Ex. 3, at A884; (2) stated in its clinical overview that "fractures with similar clinical features had previously been reported in patients not taking Fosamax," *id*. at A881; (3) "identified risk factors that

simply were not associated with [atypical femoral fractures]," *id*.; and (4) failed to provide "additional information" after receiving the CRL in May 2009, "should have provided [the clarification which came from the September 2010 Task Force Report] much earlier," and "rebuffed the FDA's repeated pleas for further engagement" prior to the Task Force Report. Pl. Br., at 33-34. Based on the record before me, I disagree, and I address each of these, individually.

Pathogenesis. Plaintiffs first argue that Defendant did not provide the FDA with any possible pathogenesis, the manner of development of a disease, for atypical femoral fractures. The record belies this assertion. Defendant *repeatedly* indicated how Fosamax might cause the very injury Plaintiffs suffered. *See, e.g.*, Def. Br., Ex. 1, at A2757 (mentioning "[s]everely suppressed bone turnover"); *id*. at A2754 (describing "bone biopsy results" which "indicated low bone turnover"); Def. Rep. Br., Ex. 14, at A2597 (explaining, in its safety update, that the attached studies "related [atypical femoral fractures] to severely suppressed bone turnover that may develop during long-term" Fosamax use). In fact, in clinical trials three decades ago, Defendant informed the FDA that "antiresorptive agents may inhibit microdamage repair by preventing . . . bone resorption at the sites of microdamage," *Fosamax*, 852 F.3d at 275 (citing A1774), which was borne out to be the correct pathogenesis according to Plaintiffs' own experts. *Id*., Ex. 3, at A880 ("[D]ecreased bone toughness can lead to stress fracture. Fosamax and other [bisphosphonates] can reduce the body's ability to repair a stress fracture once it has begun, prior to complete fracture. This might explain why a large

number of bisphosphonate-induced stress fractures go on to completion."). Indeed, on appeal, the Third Circuit acknowledged that "Merck kept the FDA informed" of the "scores of case studies, reports, and articles … published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." *Fosamax*, 852 F.3d at 275. Plus, the FDA itself has since agreed that Merck "provided [the Agency] with the relevant scientific data about Fosamax's risks." FDA Brief as *Amicus Curiae*, at *14.[15] Thus, based on the record, this argument lacks merit.

Clinical Features. Plaintiffs next argue that Defendant's clinical overview indicated that some clinical features associated with Fosamax use presented in patients not taking Fosamax. To be clear, the PAS stated, in this regard, only that "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates." Based on this solitary statement, Plaintiffs suggest that by failing to communicate the "unique features" of atypical femoral fractures to the FDA, in particular, their "fracture pattern," Defendant created a misleading impression that such fractures are "much more common in the absence of [bisphosphonates]" than they actually are. Pl. Opp. Br., at 32.

Upon closer examination of the PAS's clinical overview, however, the Court does not find Defendant's submission misleading, deceptive, or ambiguous in any way. While the clinical overview

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[15] The Court notes that the FDA filed this brief as *amicus curiae* in support of Defendant in *Merck*.

identified that the fractures at issue here occur in a similar population of elderly individuals as other osteoporotic low-energy fractures, it also explained that "these [atypical femoral] fractures are *less common than other osteoporotic low-energy fractures*," and only represent "about 6% of fractures of the femur." In other words, Defendant informed the FDA that atypical femoral fractures are rare—even in elderly individuals who are taking Fosamax, and in that regard, there is no evidence in the record of Defendant "hiding-the-ball," as suggested by Plaintiffs. Moreover, while Plaintiffs take issue with the fact that the clinical overview states that atypical femoral fractures have been reported in patients not taking bisphosphonates, they fail to acknowledge the significant fact that the FDA-mandated warning *itself* observed that atypical femoral fractures occur in "osteoporotic patients who have not been treated with bisphosphonates." Indeed, all along, the FDA questioned whether taking bisphosphonates for a prolonged period of time would actually lead to more atypical femoral fractures because other osteoporotic patients, who were not on such therapy, also suffer from the same fractures. This is the very causation-related concern that led the FDA to reject Merck's PAS in the first place. *See infra*. In the end, even though the FDA approved an amendment regarding atypical femoral fractures, the warning includes the observation that osteoporotic patients, generally, have suffered such fractures. This fact, alone, dooms Plaintiffs' claim that Defendant misled the FDA by pointing out the same.

False Risk Factors. Plaintiffs contend further that Defendant emphasized "false risk factors" in materials

sent to the FDA, the implication being that Merck "attempted to confound the true nature of the association between Fosamax and [atypical femoral fractures]." Pl. Br., at 32. Specifically, Plaintiffs argue that when the Task Force examined the actual data, some of the risk factors identified in the clinical overview and Defendant's proposed warning, namely, "abnormally decreased bone mineral density associated with osteoporosis, long-term immobilization/disuse, and use of glucocorticoids, the presence of joint deformity, leg-length discrepancies, muscle weakness, and spasm with resulting alteration in force distribution across the joints," "simply were not associated with [atypical femoral fractures]." *Id*., Ex. 3, at A882-83.

But, Plaintiffs misconstrue the language of the PAS to support their position. Rather, the "Spontaneous Reports" section of the clinical overview examined 132 reports where alendronate therapy was given for treatment of several conditions, looking specifically for evidence and information related to fractures. In part, it also discussed fracture risk factors, noting that 70 of the 132 reports provided sufficient information on the patient's medical history, concurrent conditions, and concomitant medications. In that regard, however, the clinical overview did not express any conclusions, nor did it make any pronouncements. Instead, it provided a laundry list of pre-existing conditions, comorbidities, and other attributes, along with the percentage of the 70 patients whose medical history reported those conditions. Specifically, the clinical overview stated that musculoskeletal disorders, including osteoarthritis and rheumatoid arthritis, were reported in 38 of the 70 patients; the "presence of joint

deformities, muscle imbalance, leg-length discrepancies, and change in activity" were "common" for this subgroup of patients; and 28 of the 70 patients had a history of fracture. Indeed, the clinical overview also highlighted that only 10 of the 70 patients sustained atypical fractures following joint replacement or surgery, 17 patients had endocrine or metabolic disorders like diabetes mellitus and obesity, 10 patients reported malignant disease, and 3 patients were smokers. Thus, the purpose of the "Spontaneous Reports" section of the clinical overview was not to provide a definitive list of risk factors, but rather to provide a complete picture of the clinical landscape to physicians prescribing Fosamax. Def. Br., Ex. 1, A2754-A2756. It was not meant, as Plaintiffs have advanced, to obfuscate the seriousness of potential injuries or to mislead the FDA. The record reflects that Defendant clearly appreciated the seriousness, and sought to alert the FDA, of these fractures on numerous occasions. *Id*. at A2756 ("[C]onsidering the clinical importance of these fractures . . . it is important to include an appropriate statement about them."). More compelling, the Task Force Report also concluded that certain fracture risk factors, unrelated to bisphosphonate use, exist; the Report specified that comorbid conditions are "Minor Features" of atypical femoral fractures, making them *relevant* rather than irrelevant. *See infra*.

Failure to Provide Additional Information. Finally, Plaintiffs assert that Defendant deprived the FDA of relevant information between 2008 and 2009, such as information that the Task Force eventually reported, leaving the agency "uncertain about the nature of atypical femoral fractures" and "[d]elayed by

[Defendant's] inaction." Pl. Opp. Br., at 34. This argument also lacks merit. For one, Plaintiffs do not point to any specific instance in which Defendant failed to provide any timely and relevant information, data, case studies, or evidence to the FDA, or rebuffed a request for further engagement. While Plaintiffs make much of Defendant's decision to withdraw its PAS instead of applying for a formal meeting, they ignore the fact that Defendant did so at the FDA's direction, Def. Br., Ex. 3, at A1498, that it was entitled to do so by statute, 21 U.S.C. § 314.70(c)(6)(iii)(A), and that it subsequently stated in its CBE amendment to the Adverse Reactions section that it *still* wished to discuss a Precautions warning. *Id.*, Ex. 4, A2963-64 ("Merck believes that further discussion with regard to text for the Precautions section of the label . . . would be beneficial."). Likewise, Plaintiffs' contention that, Defendant should have provided the additional information contained in the Task Force Report before the Task Force independently reviewed it, fails. The Task Force relied on 24 new case studies and 63 new articles *after* the FDA issued its CRL, according to Plaintiffs' own experts. Pl. Br., Ex. 3, at A879 ("In 2008 [at the time of the PAS], 13 of [ ] 37 published case series and reports [cited by the Task Force] were available to Merck. By May of 2009, 19 of [ ] 37 published case series were available to Merck. Additionally, the Task Force cited a total of 177 published or available articles and posters. Of those 177, 114 were available in 2008 [at the time of the PAS] or earlier and 120 were available before May of 2009."). Additionally, Defendant knew that the FDA, outside experts, and other manufacturers were working "closely" during this period to study atypical

femoral fractures, which obviated the need to continue forwarding piecemeal research, *see, e.g.*, Pl. Br., Ex. 18, at A1508, particularly since the FDA specifically informed Merck that the Agency will continue to independently study and investigate the issues.

If any doubt remains as to whether Defendant fully informed the FDA of the justification for its warning, the Agency itself agrees that Defendant "provided [it] with the relevant scientific data about Fosamax's risks." FDA Brief as *Amicus Curiae*, at *14. Because the FDA alone is the "arbiter of which data and information is or is not 'material' to [its] decision to approve or reject a change to a drug's label" under *Merck*, the FDA's view of the evidence matters.[16] *In re Avandia*, 945 F.3d at 759. Accordingly, I conclude that Defendant has satisfied the first *Merck* prong.

C. *Prong 2 of Impossibility Preemption*

As to the second prong of preemption, the crux of the parties' dispute is whether the FDA informed Defendant that it would not approve changing Fosamax's label to add the warning required by state law. Arguing in the negative, Plaintiffs advance two reasons why: (1) the CRL does not carry preemptive effective because it is not a final agency action, and (2) the FDA rejected Defendant's proposed warning for emphasizing "garden variety" stress fractures, not because it disagreed with the underlying science linking Fosamax use to atypical femoral fractures; in

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[16] Because I conclude that Defendant fully informed the FDA of the justifications for its warning, I need not address Defendant's contention that Plaintiffs "waived any contrary argument [on this issue] several times over" by not raising it on appeal. Def. Br., at 20.

that regard, Plaintiffs claim that the Agency might have approved some other version of the warning had Defendant proposed one. I will address each, in turn.

i. *The Preemptive Effect of the CRL*

Plaintiffs argue—for the very first time in this long-pending MDL—that the CRL is not preemptive because it is not a final agency action which consummates the FDA's decisionmaking process. Pl. Br., at 12-14.

The Supremacy Clause grants "supreme" status only to the "the Laws of the United States." U.S. CONST. ART. VI, CL. 2. "Nothing short of federal law can have that effect." *Fellner*, 539 F.3d at 243; *Gibbons v. Ogden*, 22 U.S. 1 (1824). Federal agency actions can constitute "Laws" in the sense of the Supremacy Clause. *Hillsborough County*, 471 U.S. at 713 ("[S]tate laws can be preempted by federal regulations as well as by federal statutes."); *New York v. Fed. Commc'n Comm'n*, 486 U.S. 57, 63 (1988) ("The phrase 'Laws of the United States' [in the Supremacy Clause] encompasses both federal statutes themselves and federal regulations that are properly adopted in accordance with statutory authorization"). However, this applies "only when [ ] [the agency] is acting within the scope of its congressionally delegated authority, . . . for an agency literally has no power to act, let alone pre-empt the validly enacted legislation of a sovereign State, unless and until Congress confers power upon it." *New York v. FERC*, 535 U.S. 1, 18 (2002) (quotations and alterations omitted); *Fidelity Fed. Savings and Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153-54 (1982).

Relying on Justice Thomas' concurrence, Plaintiffs argue that the CRL does not carry preemptive effect because it is not a final agency action. Pl. Br., at 27-28. According to Plaintiffs, the CRL does not mark "the consummation of the agency's decisionmaking process," *Bennett v. Spear*, 520 U.S. 154, 178 (1997) (quotations omitted), finally determine the parties' "rights or obligations," or impose "legal consequences." *Port of Boston Marine Terminal Assn. v. Rederiaktiebolaget Transatlantic*, 400 U.S. 62, 71 (1970). This argument is misplaced for several reasons. To begin, the majority in *Merck* explicitly cited 21 C.F.R. § 314.110(a), which empowers the FDA to "formally reject" a drug manufacturer's proposed warning through a CRL, as an example of an FDA action that *does* constitute "Law" in the sense of the Supremacy Clause. 139 S.Ct. at 1679. That should end the inquiry.

In any event, Plaintiffs' position appears to confuse the question whether an agency action is final—for example, for the purposes of providing judicial review under the Administrative Procedures Act, *Port of Boston*, 400 U.S. at 71—with the question of whether the agency action is "Law" with the power to preempt. These are distinct inquiries and have different legal consequences. The preemption question turns on whether Congress delegated to the agency the authority to act in such a manner in the first instance, not on whether the agency's action is necessarily a "final" one. *FERC*, 535 U.S. at 19 ("This sort of case . . . defining the proper scope of federal power . . . requires us to be certain that Congress has conferred the authority."). The yardstick is congressional intent, not the finality of its action. *See, e.g., English v.*

General Elec. Co., 496 U.S. 72, 78-79 (1990) ("[P]reemption fundamentally is a question of congressional intent."); *Medtronic*, 518 U.S. at 485 ("'The purpose of Congress is the ultimate touchstone' in every preemption case.") (quoting *Retail Clerks v. Schermerhorn*, 375 U.S. 96, 103 (1963)); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516, 530 n.27 (1992) (holding that the scope of preemption must rest "on a fair understanding of congressional purpose"); *Malone v. White Motor Corp.*, 435 U.S. 497, 504 (1978) ("It is uncontested that whether [the statute at issue is preempted] depends on the intent of Congress."); *Louisiana Pub. Serv. Comm'n v. FCC*, 476 U.S. 355, 374 (1986) (stating that the best way to determine preemption "is to examine the nature and scope of the authority granted by Congress to the agency").

It follows that for preemption purposes, it is mostly irrelevant whether the CRL is "of a merely tentative or interlocutory nature," *Bennett*, 520 U.S. at 178, or that it simply "informs sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application." 73 Fed. Reg. 39588. As Defendant points out, Def. Rep. Br., at 11-12, if Plaintiffs' position were to prevail, no CRL could ever carry preemptive effect because all CRLs require some subsequent action on the part of the manufacturer, and preserve some procedural mechanism to further engage with the FDA, even if futile. 21 C.F.R. § 314.110(b) (providing three options: "[r]esubmit the application . . . , addressing all deficiencies identified in the [CRL]," "[w]ithdraw the application . . . without prejudice to a subsequent submission," or "[a]sk the agency to provide . . . an opportunity for a hearing," after which

"the agency will either approve" or "refuse . . . the application"). And, more importantly, it would abrogate the very preemption effect of the federal regulation, 21 C.F.R. 314.110(a), that the FDA promulgated pursuant to congressional authority. For these reasons, I reject Plaintiffs' claim that the CRL does not have preemptive effect under the Supremacy Clause. I turn, next, to the content of the CRL.

ii. *The CRL*

The parties dispute how to construe the meaning, and impact, of the CRL, which centers on four issues: (1) whether Defendant proposed an adequate warning; (2) whether the contents of the CRL, alone, support the inference that the FDA rejected Defendant's warning based on the Agency's belief that the underlying science did not justify one; (3) if the CRL does not convey such an inference on its face, whether the CRL, when construed in addition to the FDA's other communications from the same time period, support that inference; and (4) how the surrounding regulatory regime informs the CRL. Plaintiffs posit that Defendant's warning was inadequate under state law, and the FDA rejected it merely because of the general "stress fractures" language, which does not indicate whether a differently worded warning would have been accepted by the FDA. Defendant, on the other hand, maintains that it sought to warn of the very injury Plaintiffs suffered, and the CRL—construed either on its own or in light of the FDA's other communications—prohibited Merck from adding any and all warnings to the Fosamax label because the Agency seriously questioned, and therefore doubted, a causal connection between bisphosphonates and atypical femoral fractures.

1. Adequacy of Defendant's Proposed Warning

To show that the FDA rejected a warning that would have been adequate under state law, Defendant must first establish that it actually proposed such a warning, an implicit but critical step in the analysis. Plaintiffs insist that Defendant failed to do so, because Defendant merely proposed "garden variety" stress fractures in its language, rather than atypical femoral fractures, despite scientific evidence allegedly differentiating between the two. Pl. Br., at 1, 5, 16. Plaintiffs point to the text of the warning as support: "every sentence after the first sentence described . . . 'stress fractures'" not "atypical" fractures, *id*. at 17, the warning referenced "similar clinical features" in fractures in "patients not treated with bisphosphonates," and Defendant suggested evaluating patients for other "known causes and risk factors," in addition to bisphosphonate use.

Defendant responds that it "tried to warn of the precise low-energy fractures that Plaintiffs allegedly suffered." Def. Rep. Br., at 5. In its proposed warning, Defendant highlights that it emphasized the essential features of atypical femoral fractures even if it did not use the term "atypical." *Id*. Defendant also points to "the warning that the FDA mandated following the Task Force Report," which conveys similar information as Defendant's proposed one, *id*. at 8, and which Plaintiffs concede is adequate. Pl. Br., at 10. Finally, Defendant notes communications with the FDA characterizing the warning as pertaining to "atypical . . . fractures," Def. Br., Ex. 2, at A1500; Pl. Br., Ex. 10, at A1145, and expert testimony that it "approach[ed] the FDA with respect to [such]

fractures." Def. Rep. Br., at 8; Def. Br., Ex. 3, at A1498; *id*., Ex. 15, at 660.

As an initial matter, Plaintiffs raised this argument before Judge Pisano to no avail. *Glynn*, 951 F. Supp. 2d at 701 (rejecting position that "the FDA rejected the PAS because [Defendant] used the phrase 'stress fracture' instead of 'atypical' fracture, and the FDA would have approved an appropriately worded warning"). After hearing expert testimony from both parties on the relevant terminology, Judge Pisano found Defendant's warning to contain "the same language" that Plaintiffs contend state law requires. *Id*. at 703-04.

I reach the same result upon a fresh review of the record. To reiterate, Merck proposed adding the following language to the Precautions section:

> ***Low-Energy Femoral Shaft Fracture***
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption,

> glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pl. Br., Ex. 38 at A1371. To begin, I refer to the science regarding bone resorption and formation. All bones, whether healthy or osteoporotic, can develop microscopic cracks—called stress fractures—from everyday activity. These "ordinarily heal on their own through the bone remodeling process." *Merck*, 139 S.Ct. at 1673. When that process is disrupted, from a bisphosphonate for example, the body may not naturally repair itself, creating stress fractures as a result. Relevant here, stress fractures may then progress to atypical femoral fractures, or complete breaks of the femur, which cause pain and require surgery rather than rest. Stated differently, atypical femoral fractures *are* stress fractures, but more severe than other types of stress fractures, such as those that heal on their own. Shane et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research*, 29 J. Bone & Min. Res. 1, 12 (2014) (concluding same). Plaintiffs all but concede this point: atypical femoral fractures "start as . . . stress fractures." Pl. Br., Ex. 4, at 12.

It is also important to consider the Task Force Report, which defined key characteristics of, and risk factors for, atypical femoral fractures. The Task Force listed "Major Features," which are necessary to

diagnose a patient with an atypical femoral fracture, and Minor Features, which may be associated with such a fracture but are not required characteristics. As to the Major Features, the fracture is (1) "located anywhere along the femur from the distal to the lesser trochanter to just proximal to the supracondylar flare"; (2) "associated with no trauma or minimal trauma"; (3) transverse or short oblique in configuration; (4) noncomminuted, meaning that there are not multiple breaks; and (5) complete in that it extends through both cortices and may be associated with a medial spike. The Minor Features are: (1) localized periosteal reaction of the lateral cortex; (2) generalized increase in cortical thickness of the diaphysis; (3) prodromal symptoms such as dull or aching pain in the groin or thigh; (4) bilateral fractures and symptoms; (5) delayed healing; (6) comorbid conditions (*e.g.*, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia); and (7) use of pharmaceutical agents (*e.g.*, bisphosphonates, glucocorticoids, and proton pump inhibitors). Shane et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research*, 25 J. Bone & Min. Res. 2267, 2268-69 (2010).

Having set forth the foundational science, I turn to the proposed warning. First, Plaintiffs argue that the title "Low-Energy Femoral Shaft Fracture" references "a broad category" of fractures including "[atypical femoral fractures] and less serious fractures," Pl. Br., at 17 n.3, and thus, does not constitute an adequate warning. I disagree. The title itself describes aspects of an atypical fracture, that is, it occurs from minimal trauma (*i.e.*, low-energy) and in a discrete part of the

thigh bone (*i.e.*, the femoral shaft), which, according to the Task Force, are the two Major Features of atypical femoral fractures. This is consistent with the Patient Packet Insert for Fosamax, which alerts patients that some users "have experienced fracture *in a specific part of the thigh bone*." Def. Br., Ex. 1, at A2742 (emphasis added). The first sentence of the warning then describes that the type of fracture at issue, or the subject of the warning, occurs in the "subtrochanteric and proximal" region of the "femoral shaft," which is another Major Feature identified in the Report, and a distinguishing characteristic according to Plaintiffs' own brief. Pl. Br., Add. 8 (containing an x-ray image of an atypical femoral fracture displaying these features); *id.*, Ex. 2, at A1148-49 (explaining that atypical femoral fractures are distinguishable, in part, because they occur "perpendicular to the femoral shaft" and in "the proximal (upper) third . . . or the subtrochanteric region").

Next, the warning advises that "[s]ome" low-energy femoral shaft fractures "[are] stress fractures." Plaintiffs interpret this sentence as conflating garden variety stress fractures with atypical femoral fractures, despite a distinction between them. Pl. Br., at 32 ("Merck improperly conflated the underlying fracture mechanism that leads to [atypical femoral fractures] with the ultimate outcome."). I do not see any basis in the science for such a strict dichotomy. As discussed *supra*, atypical femoral fractures *are* stress fractures, just severe ones and located in a particular part of the body, exhibiting a difference in degree but not necessarily in kind. *Merck*, 139 S.Ct. at 1674 (stating that atypical femoral fractures "progress" from microscopic stress fractures); *Glynn*, 951 F. Supp.

3d at 704 (quoting one of Plaintiffs' experts who testified that Fosamax "can lead . . . to subsequent stress fracture formation"). In the Task Force's own words, "[t]he radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures." Shane et al., at 2270. In addition, in Plaintiffs' expert's words, "decreased bone toughness can lead to stress fracture. Fosamax and other [bisphosphonates] can reduce the body's ability to repair a stress fracture once it has begun, prior to complete fracture. This might explain why a large number of bisphosphonate-induced stress fractures go on to completion." Pl. Br., Ex. 3, at A880.

On this point, Plaintiffs inexplicably overlook Defendant's PAS, which explains that Defendant uses the term "stress fracture" in its warning to mean an "insufficiency fracture" that occurs with no "identifiable external traumatic event." Def. Br., Ex. 1, at A2751-52. While the term "stress fracture" often, in generic terms, "connotes a fracture resulting from excessive loading of a normal bone," as is common in athletes, an "insufficiency [ ] fracture" is a specific *type* of stress fracture "caused by normal loading of poor-quality bone," as allegedly happened to Plaintiffs after taking Fosamax and about which Defendant sought to warn. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 710-11 (29th ed. 2000) (defining an "insufficiency f[racture]" as "a stress fracture that occurs during normal stress on a bone of abnormally decreased density"). Defendant's PAS goes on to state that 91% of the fractures discussed therein, and referenced in the warning, resulted in surgical intervention, while the other 9% involved patients who sustained only "incomplete stress fractures," Def. Br., Ex. 1, at

A2755, which further distinguishes the warned-of injury from the garden variety type.

Next, Plaintiffs cite an internal email between Merck colleagues from December 19, 2010, in which several Merck employees shared redline revisions to rationales for their proposed changes to the Fosamax label. Pl. Br., Ex. 27, at A1573. Within those rationales, Defendant states that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." *Id*. Plaintiffs offer this as "belated" evidence that Defendant knew its "proposed focus on stress fractures [in 2008] would confuse general physicians." Pl. Br., at 18. Having reviewed the email, such an inference cannot be drawn. Setting aside the questionable relevance of internal correspondence regarding the *FDA-mandated* label change over two years later, read in context of the email, Defendant's statement sought to *clear up* any confusion by suggesting that physicians *rule out* common causes before diagnosing a rarer atypical femoral fracture. Indeed, as the warning stated, because "[t]he number of reports of this condition is very low," patients should "be evaluated . . . for known causes and risk factors." This mirrors the Task Force's own determination two years later that atypical femoral fractures occur with "relative rarity" and may be "associated" with "comorbid conditions." Pl. Br., Ex. 2, at A1147.

Furthermore, Plaintiffs make much of the fact that atypical femoral fractures tend to "cause great pain," Pl. Br., at 5 (quoting *Merck*, 139 S.Ct. at 1674); *id*. at 6 (describing them as "debilitating"); *id*. at 17 (same,

but "gruesome"), and they contrast this fracture with garden variety stress fractures, which usually heal themselves with rest and presumably do not cause much pain. *Id.* at 18. Plaintiffs argue that the lack of language regarding severe pain in Defendant's warning is evidence that Defendant was describing garden variety stress fractures. But Plaintiffs' position is belied by: (1) the Task Force's finding that such pain is a "Minor Feature," not a required characteristic; (2) Defendant's warning indeed provides that "[s]ome patients experience[] prodromal pain in the affected area" in any event, which suffices to capture any potential pain-related difference between atypical femoral fractures and garden variety stress fractures; and, most importantly, (3) the FDA-mandated label includes an almost identical statement, which Plaintiffs concede is adequate under state law. Def. Br., Ex. 7, at A1516-17. Further consistent with this purported feature of atypical femoral fractures, the Patient Package Insert instructs patients to "[c]all your doctor if you develop new or *unusual* pain in the hip or thigh." Def. Br., Ex. 1, at A2742 (emphasis added).

Relatedly, Plaintiffs emphasize the difference between "the nature" of garden variety stress fractures, which are "barely perceptible," and atypical femoral fractures, where "the thigh bone (the largest and strongest bone in the body) looks like a pencil snapped in two. " Pl. Br., at 18; *compare id.*, Add. 8 (containing an x-ray image of an atypical femoral fracture), *with id.*, Add. 7 (containing an x-ray image of a microscopic stress fracture). Again, however, Plaintiffs' argument that Defendant glossed over this unique feature of atypical femoral fractures in their

warning lacks merit. Significantly, Defendant's warning explicitly describes "a complete fracture," a phrase that appears in the FDA-mandated label as well. The warning also cautions that such injuries can occur "weeks to months" after "prodromal pain . . . associated with imaging features of stress fracture." The term "prodromal" denotes a transitory phase between the appearance of an initial symptom—*i.e.*, a stress fracture—and the full development of a condition—*i.e.*, "a complete fracture" of the thigh bone. To that extent, the warning captures the progression from microscopic fracture to total shaft fracture that defines the relationship between bisphosphonates and atypical femoral fractures, and the impact Fosamax may have on this type of fracture overtime. *See* Pl. Br., at 32; *id.*, Ex. 3, at A880 ("Fosamax and other [bisphosphonates] can reduce the body's ability to repair a stress fracture once it has begun, prior to complete fracture.").

Additionally, Plaintiffs focus on another portion of Defendant's warning: "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates," which "threaten[s] to mislead physicians [and the FDA] about the nature of the relevant risk." Pl. Br., at 18. As stated *supra*, I do not find this misleading, because the statement clarifies and underscores the rarity of atypical femoral fractures. In any case, according to the Task Force Report, the "nature of the relevant risk" *can* include comorbid conditions, which are a Minor Feature. Likewise, Plaintiffs offer nothing to reconcile their position with the fact that the FDA-mandated warning contains precisely the same statement—"these fractures also occur in osteoporotic patients who have

not been treated with bisphosphonates." Def. Br., Ex. 7, at A1516-17. If the FDA warning is adequate, as Plaintiffs acknowledge, so must be the warning proposed by Defendant in this regard.

Finally, and more compellingly, regardless of any inadequacies in the text of Defendant's warning, the FDA clearly understood the type of fracture at issue. In a June 2008 email titled "Fosamax Information Request – Atypical Fractures," the Agency asked Defendant for more data concerning "the occurrence of atypical fractures." Pl. Br., Ex. 10, at A1145. Then, in an email from April 2009, the FDA described Defendant's PAS as the "currently pending [Supplemental Label Revision] for atypical fracture," and stated that it would likely approve "atypical fracture language" in the "postmarketing adverse events section of the label" only, Def. Br., Ex. 3, at A1498, which led to expert testimony at trial concluding that Defendant "approach[ed] the FDA with respect to atypical femur fractures" in 2008. Def. Br., Ex. 15, at T660:5-8. What is more, the FDA even called the fractures at issue "atypical" in its CRL, Def. Br., Ex. 2, at A1500; *id*., Ex. 1, at A2751-52 (defining how the PAS uses the term stress fracture for the FDA, and distinguishing garden variety stress fractures), and stated in its October 2010 Safety Announcement that it had been studying "atypical" fractures all along.

Plaintiffs' only response to this evidence[17] can be distilled down to a single point: Defendant did not use

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[17] As discussed more fully, *infra*, this type of evidence, including email communications, may be considered by the Court in examining the CRL.

the word "atypical" in its proposed warning. Not only is a terse and superficial interpretation of the text, but as Judge Pisano observed, and I agree, "atypical" was hardly settled scientific jargon at the time. *Glynn*, 951 F. Supp. 3d at 704 (quoting one of Plaintiffs' trial experts who was "central" to their preemption argument, and who said that word was not "contrived" until about 2010). While this non-material characterization makes Defendant's warning different from the FDA-mandated warning, it does not make the warning any less adequate under state law, nor does it create the inference that Defendant misunderstood or miscommunicated the underlying science. To the contrary, Defendant's warning describes how/when atypical femoral fractures occur (low-energy events in the absence of trauma), where they occur (to the subtrochanteric and proximal femoral shaft), their nature (complete fractures), their progression (they develop out of garden variety stress fractures), and their severity (they can be associated with prodromal or unusual pain). Indeed, as explained *supra*, in this context, "atypical" is virtually synonymous with the term "low-energy" to describe the femoral fractures at issue. Accordingly, the warning had all the hallmarks of atypical femoral fracture such that not having employed the word "atypical" would not somehow change the nature of the proposed warning as plainly expressed by its language.

2. The Language of the CRL

Next, Plaintiffs argue that the CRL, by its terms, rejected Defendant's proposal based on language used, not on the fact that the FDA was unconvinced of a causal relationship between atypical femoral fractures and bisphosphonate. Pl. Br., at 19. Plaintiffs rely on

the text of the letter to make this point, which, in Plaintiffs' view, does not expressly reference any disagreement with the evidence linking atypical fractures to bisphosphonates. They also emphasize that Defendant's litigation position differs from its own scientists' "contemporaneous reading of the [CRL]." *Id.*, Ex. 29, at A1506; *id.*, Ex. 30, at A1504; *id.*, Ex. 17, at T265:12-18. Specifically, Plaintiffs point out that the day Defendant received the CRL, its Director of Clinical Research, Arthur Santora, interpreted it to convey that the "FDA wouldn't let [Merck] mention stress fractures." *Id.*, Ex. 29 at A1506. That same day, Plaintiff highlights that Defendant's U.S. Regulatory Liaison, James Adams, informed his colleagues that the FDA "believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures." *Id.*, Ex. 30 at A1504. According to Plaintiffs, however, Adams later testified that the CRL does not mention any belief that "there was insufficient evidence to establish a causal association between Fosamax and atypical femur fractures." *Id.*, Ex. 17.

Defendant insists that FDA rejected its proposed warning in the CRL because "the data was not yet sufficient to allow for [such a warning]," rather than because the Agency disagreed with Defendant's wording. Def. Br., at 27. Like Plaintiffs, Defendant points to the text of the CRL, which states that the "justification" for the warning was "inadequate." Defendant reads this as "a commentary on the absence of a sufficiently clear link between Fosamax and the atypical fractures at issue." *Id.* And, because the CRL rejected Defendant's warning for "reasons," plural, the

FDA could not have opposed the "stress fracture" language, alone. Def. Rep. Br., at 9.

The CRL was a response to Defendant's PAS, which, as discussed *supra*, sought to include a proposed warning that advised patients of the risk of developing atypical femoral fractures by taking Fosamax. In that regard, the CRL begins by describing Defendant's proposal as "adding language to the PRECAUTIONS section and the ADVERSE REACTIONS, Post-Marketing Experience subsection of the Package Inserts (Pls) *to describe low energy fractures at the* subtrochanteric region of the femoral shaft. In addition these supplements propose adding language describing this type of fracture in the Patient Package Insert (PPIs)." Def. Br., Ex. 2, at A1500 (emphasis added). The FDA rejected Defendant's proposal for amending the Precautions section, explaining:

> While the Division agrees that atypical and subtrochanteric fractures should be added to the ADVERSE REACTIONS, Post-Marketing Experience subsections of the FOSAMAX Tablets and Oral Solution and FOSAMAX Plus D Tablets labels, your justification for the proposed PRECAUTIONS section language is inadequate. *Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature.* Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.
>
> *Id*. at A1500-01 (emphasis added).

I appreciate that, as worded, the language of the CRL gives rise to competing inferences with respect to why the FDA rejected Defendant's warning. On the one hand, the CRL describes the "justification" for the warning as "inadequate." Logically, the CRL was presumably referencing the data Defendant submitted with its PAS, linking low-energy femur fractures to bisphosphonates. On the other hand, the CRL discusses Defendant's use of the term "stress fracture," stating that such fractures "may not be clearly related to the atypical . . . fractures that have been reported in the literature" and it is "not warranted" to discuss risk factors for them. Def. Br., Ex. 2, at A1500-01. In light of these competing readings, I must look beyond the CRL's terms alone to ascertain its meaning and scope.

3. The FDA's Communications from the Same Time Period

If the CRL were the sum total of the evidence of FDA action in this case, Plaintiffs might be on firmer footing with regards to their preemption arguments. But, Defendant points to various communications from the FDA during the same time period to "understand what the FDA *action* [*i.e.*, CRL] meant." Def. Rep. Br., at 10. For instance, in April 2009, a month before the CRL, agency officials wrote that "the conflicting nature of the literature does not provide a clear path forward" on the question whether to add a warning to the Precautions section, Def. Br., at 26; Pl. Br., Ex. 33, at A1970-71, and "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution around these data." Pl. Br., Ex. 12, at A1498; *id.*, Ex. 33, at A1970-71. As

stated, *supra*, the data specifically involves atypical femoral fractures.

Then, in March 2010, the Agency stated that its review of the data "did not show an increase in th[e] risk" of atypical femoral fractures from bisphosphonate use. Def. Br., Ex. 5, A1508. FDA officials did not change their assessment until October 2010, a month after the Task Force issued its Report, *id*., Ex. 10, at A1118-19; *id*., Ex. 6, at A1392-93, which "clarif[ied] the features of atypical femoral fractures," Pl. Br., Ex. 20, at A1392, and "help[ed] the [Agency] understand [them] a little bit better." *Id*. at A1396. But even then, the FDA did not observe a definitive causal link. Indeed, this series of events would not have occurred "if the agency already had a sufficient basis, in May 2009, to approve a warning" in the Precautions section. Def. Br., at 26. Neither would the FDA's own interpretation of the CRL in this litigation: it rejected Defendant's warning for "the lack of adequate data to support [it]," not "because of . . . the term 'stress fractures.'" FDA Brief as *Amicus Curiae*, at *31-32. Nevertheless, Plaintiffs argue that the FDA's informal email communications are not "Laws" in the sense of the Supremacy Clause, and in any event, Defendant "ignores the full context of what [the] FDA told [it]" at the time. Pl. Br., at 25.

Plaintiffs are correct that informal communications do not constitute "Laws" with the power to preempt. *In re Avandia*, 945 F.3d at 760 (holding that "an informal phone conversation with an FDA official is not an 'agency action taken pursuant to the FDA's congressionally delegated authority'") (quoting *Merck*, 139 S.Ct. at 1679). Yet, importantly, Defendant does not argue that the FDA's informal communications

themselves establish preemption, only that they "shed light on" the meaning and scope of the CRL, which *is* "Law" with preemptive effect. Def. Br., at 30. I agree that it is appropriate to consider the communications for that limited purpose. *See, e.g., Fosamax*, 852 F.3d at 293 (stating that the preemption inquiry involves an "evaluative inference about human behavior based on correspondence[] [and] agency statements"); Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019) (remanding to this Court "to determine the effect of the FDA's [CRL] and other communications"); Center for Drug Evaluation & Research, FDA, *CDER 21st Century Review Process: Desk Reference Guide* 37 (2014) (explaining that the "[d]evelopment of final labeling" is "an iterative process between the applicant and FDA" involving significant correspondence); FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* 21 (Apr. 2005) (addressing "communication between the FDA and applicants" during "labeling discussions"); 21 C.F.R. § 10.85(k) (providing that an FDA employee's written statement, which constitutes "an informal communication," "does not *necessarily* represent the formal position of FDA," a statement that by its terms contemplates that certain employee statements *may* do so); *In re Incretin*, 2021 WL 880316, at *16-17 (considered and credited such evidence); *Swanson v. Abbott Lab'ys*, No. 14-1052, 2017 WL 5903362, at *4 (S.D. Ohio Nov. 28, 2017) (same). Indeed, in Justice Alito's concurrence here, he suggested that informal communications between the FDA and drug manufacturers should be considered in the preemption analysis. *Merck*, 139 S.Ct. at 1685; *see*

In re Zofran (Ondansetron) Prods. Liab. Litig., 541 F. Supp. 3d 164, 194 (D. Mass. 2021).

Focusing on the sequence of communications and announcements from the same period, the CRL does not tell the whole story without the proper context gleaned from other FDA communications. The FDA received data regarding atypical femoral fractures long before 2008, and specifically sought more information in June 2008 on "atypical femoral subtrochanteric femur fractures," a request with which Defendant complied. Def. Br., Ex. 5, at A1508 ("All available case reports and clinical trial data were requested."); *Fosamax*, 852 F.3d at 296 ("It is undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010."). Defendant proposed amending both the Precautions and Adverse Reactions sections of the Fosamax label in September 2008, to include an appropriate warning about atypical femoral fractures, which was "important" to do given their clinical significance, even if it "was not possible with the present data" to establish causation, and even if the FDA was in the process of reviewing the issue. Pl. Br., Ex. 38, at A1349; Def. Br., Ex. 1, at A2756. The FDA rejected Defendant's Precautions warning in May 2009. In correspondence before sending the CRL, agency officials stated that the "conflicting nature of the [scientific] literature does not provide a clear path forward" on a Precautions warning, "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution" based on the data, and Defendant's "elevation of [the warning]

to a precaution" was "prolonging review."[18] Pl. Br., Ex. 33, at A1971. Then, after sending the CRL, the FDA expressed no desire to consider revisions despite Defendant's repeated inquiries to that end.

As late as March 2010, the FDA continued to believe that the "available" data "did not show an increase in th[e] risk" of atypical femoral fractures from bisphosphonate use, instructed doctors to "continue to follow" the existing Fosamax label, and specifically noted a December 2008 study showing "similar numbers of atypical subtrochanteric femur fractures relative to classic osteoporosis" in patients not treated with bisphosphonates. The FDA made this Drug Safety Announcement pursuant to its Congressionally delegated authority. 21 U.S.C. § 355(r). The FDA also stated that it was "working closely with outside experts to gather additional information that may provide more insight." Def. Br., Ex. 5, at A1508. Construed in light of these various FDA communications, the CRL clearly rejected Defendant's warning, in part, because the FDA doubted the

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[18] As explained *supra*, the FDA clearly understood Defendant to be warning of the injury discussed in the literature, which is the same injury as Plaintiffs allegedly suffered. *See, e.g.*, Pl. Br., Ex. 10, at A1145 (asking Defendant for more data concerning "the occurrence of atypical fractures" in a June 2009 email titled "Fosamax Information Request – Atypical Fractures"); Def. Br., Ex. 3, at A1498 (describing Defendant's PAS as the "currently pending [Supplemental Label Revision] for atypical fracture" in an April 2009 email); Def. Br., Ex. 15, at T660:5-8 (Plaintiff's expert, Dr. Cheryl Blume, testified that Defendant "approach[ed] the FDA with respect to atypical femur fractures"); Def. Br., Ex. 2, at A1500 (calling the fractures at issue "atypical" in the CRL); Def. Br., Ex. 1, at A2752-52 (defining, for the FDA, how the PAS uses the term stress fracture).

underlying science causally connecting bisphosphonate use and atypical femoral fractures.

It is also telling that, in the process of rejecting Defendant's Precautions warning, the FDA approved an Adverse Reactions warning for "low-energy femoral shaft and subtrochanteric fractures." The reason for the Agency's decision in this regard may very well be the different causal thresholds governing each section of the label. Indeed, the Precautions section requires "*reasonable evidence* of a causal association" to add a warning about an adverse event. 21 C.F.R. § 201.57(c)(6) (emphasis added). The Adverse Reactions section requires only "*some basis to believe* there is a causal relationship." 21 C.F.R. § 201.57(c)(7) (emphasis added).

Finally, the FDA, itself, believes that it rejected Defendant's warning for "the lack of adequate data to support [it]," and not "because of . . . the term 'stress fractures.'" FDA Brief as *Amicus Curiae*, at *31-32. Plaintiffs challenge this evidence because it is a "legal interpretation[] . . . submitted by government lawyers under a subsequent administration, nearly a decade after the fact," which represents the views of the Office of the Solicitor General not the FDA. Pl. Br., at 22. I disagree on both points. First, "[I] have no reason to suspect that the Solicitor General's representation of [the FDA's] views reflects anything other than 'the agency's fair and considered judgment.'" *Geier*, 529 U.S. at 884. Second, an agency's fair and considered judgment as to the meaning of its own regulation and actions deserves some measure of deference. *Auer v. Robbins*, 519 U.S. 452, 461-62 (1997).

On the first point, it is appropriate to consider the FDA's views because Congress delegated to that agency the authority to implement federal drug regulations, it has expertise in that highly "technical" subject matter, and it is well-equipped to navigate "the relevant history and background" on such a "complex and extensive" issue. *Geier*, 529 U.S. at 883 (giving "some weight" to agency's view in a preemption case on similar grounds). Or, stated differently, the FDA is "likely to have a thorough understanding of its own regulation and objectives" with respect to any CRL it issues. *Id.; Medtronic*, 518 U.S. at 496 (relying, in part, on the FDA's interpretation of a provision's preemptive effect).

On the second point, I am not strictly foreclosed from crediting the FDA's reading of the CRL simply because the Agency advances it in litigation, particularly in light of all the other pertinent evidence. I am aware that in *Kisor v. White*, 139 S.Ct. 2400 (2019), the Supreme Court warned that "a court should decline to defer to a merely convenient litigation position or *post-hoc* rationalization advanced to defend past agency action against attack," such as a brand-new interpretation presented for the first time in legal briefs. *Id.* at 2417-18 (quotations and alterations omitted); *see also Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 155 (2012); *Bowen v. Georgetown Univ. Hospital*, 488 U.S. 204, 213 (1988). But, *Kisor* sets forth "[t[he general rule," not an "entirely foreclosed . . . practice." *Kisor*, 139 S.Ct. at 2417 n.6. For example, the *Auer* Court deferred to a "new regulatory interpretation presented in an *amicus curiae* brief in [the Supreme Court]." *Id.* Where the agency is not a party to the litigation and

has expressed its views only at the Court's invitation, as here, there is no reason to question whether it has provided its "fair and considered judgment" rather than an after-the-fact rationalization. *Id*. (citing *Auer*, 519 U.S. at 462).

In sum, when viewed in light the FDA's communications, the CRL rejected Defendant's Precautions warning because the FDA doubted the evidence linking bisphosphonate use to atypical femoral fractures in a causal sense. In other words, when it issued the CRL, the Agency believed that Fosamax's current label adequately reflected the results of the Agency's continuous and comprehensive evaluation of the risks associated with using Fosamax.

4. *The Regulatory Regime*

Finally, the parties use the regulatory regime, indeed some of the same provisions, to draw opposite inferences as to the meaning of the CRL. This is "highly relevant" and bears discussion. *Merck*, 139 S.Ct. at 1685 (Alito, J., concurring in the judgment) ("On remand, I assume that the Court of Appeals will consider the effect of [21 U.S.C. § 355(o)(4)(A)]."); *Seufert*, 187 F. Supp. 3d at 1175 ("[A] clear evidence analysis must account for the regulatory framework governing prescription drug labeling.").

Plaintiffs argue that it is "dispositive" that the FDA "omi[tted]" any explicit discussion of the science linking bisphosphonates to atypical femoral fractures, because the agency must "describe all of the specific deficiencies that [it] has identified" when it sends a CRL. Pl. Br., at 20-21; 21 C.F.R. § 314.110(a)(1). To the extent that the FDA did not specifically raise causation as an issue, it cannot form any part of the

basis for the agency's rejection, unless the agency "wrote a false [letter]." Pl. Br., at 20.

Defendant reads the regulations differently. Def. Br., at 25-27; Def. Rep. Br., at 11-12. According to Defendant, the FDA has a duty to mandate a label change if it "becomes aware of new information" that "should be included in the labeling." 21 U.S.C. § 355(o)(4)(A).[19] Defendant reasons that the FDA did not do so until October 2010, which implies that the FDA could not support a change before then and/or concluded that the Fosamax label conveyed the proper risk profile to the public at the time. Likewise, according to Defendant, the FDA will not reject a warning for "editorial" reasons, 21 C.F.R. § 314.105(b), and will "make every reasonable effort to communicate" any "easily correctable deficiencies" to a manufacturer "promptly," 21 C.F.R. § 314.102(b), including by suggesting remedies or recommending actions. 21 C.F.R. § 314.110(a). In light of these provisions, Defendant submits that based on the FDA's statutory obligations, "[h]ad the Agency believed a [Precautions] change was justified earlier," or that the problem with Defendant's warning was fixable, such as Defendant's "stress fractures" language, "it would have taken [the necessary] steps," Def. Br., at 26, similar to the steps the FDA took as to Defendant's Adverse Reactions warning, Def. Br., Ex. 1, at A2732, and when Defendant, again, proposed

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[19] Prior to October 2018, § 355(o)(4)(A)'s language contained slight differences not relevant here. *See* Substance Use-Disorder Prevention That Promotes Opioid Recovery and Treatment for Patients and Communities Act, Pub. L. 115-271, § 3041(b), 132 Stat. 3942-3943, effective Oct. 24, 2018.

stress fractures language in December 2010 in response to the Agency's mandated label.

First, while the CRL did not use certain terminology, which would have made it less ambiguous, this Court has found, *see supra*, that the CRL did in fact reject Defendant's proposed warning based on causation, and therefore, Plaintiff's argument in this context must be rejected out of hand. But, even if I were to accept Plaintiffs' position, one must assume that the FDA had reasonable evidence warranting a Precautions warning, but was so troubled by Defendant's use of the term "stress fracture" that it rejected a warning without offering any suggestions or revisions. To make such an assumption would effectively overlook the FDA's *raison d'etre* to regulate drug safety, its independent legal duty to notify a manufacturer as soon as it "becomes aware of new safety information that [it] believes should be included in the labeling of a drug" and "initiate discussions to reach an agreement . . . on labeling," 21 U.S.C. § 355(o)(4)(A), and the "presumption of regularity" accompanying its actions. Rather, "in the absence of clear evidence to the contrary, [FDA officials] have properly discharged their official duties." *United States v. Chemical Foundation, Inc.*, 272 U.S. 1, 14-15, (1926) (quoted in *Merck*, 139 S.Ct. at 1684 (Alito, J., concurring in part)). In other words, it is improbable that the FDA declined to approve Defendant's Precautions warning, or failed to propose a solution to the problem it perceived with the language, *i.e.*, stress fracture, all while the FDA had sufficient causal evidence linking bisphosphonates to atypical femoral fractures and thus exposing patients to the risk of severe injury in

the interim. *Accord Zofran*, 2021 WL 2209871, at *32 ("[T]he Court will not assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety . . . . Accepting plaintiffs' argument would suggest that the FDA . . . turned a blind eye to evidence that Zofran causes birth defects. That is highly unlikely, to say the least. And it is also unlikely . . . that it refused to take up the issue with Novartis based on the technical point that Novartis had not sought to change that specific section.").

The more likely scenario is that the FDA's *actions* taken in this case convey doubts that the Agency had about the underlying science, a deficiency *no* revision or edits could solve; hence, the Agency did not propose any. The FDA's subsequent *inaction*—it did not mandate a label change until October 2010, despite substantial ongoing review both internally and by the Task Force—confirms its then-existing perspective on the science, not that it was merely troubled by Defendant's phraseology of its proposed warning. *Ridinis v. Maurince*, No. 15-00020, 2020 WL 1264178, at *21 (W.D. Mo. Mar. 16, 2020) (holding that "continued inaction . . . in light of the known issues and the ongoing give-and-take between [a manufacturer] and the FDA" can constitute "clear evidence"); *In re Incretin-Based Therapies Prod. Liab. Litig.*, 142 F. Supp. 3d 1108, 1123-24 (S.D. Cal. 2015) ("The FDA's subsequent inaction regarding drug labeling supports the conclusion that the FDA [did] not consider available scientific evidence of a causal association sufficient to warrant inclusion in the labeling . . . . [This] is highly persuasive given the FDA's comprehensive review of pancreatic safety and

ability to mandate a label change."); *see also Merck*, 139 S.Ct. at 1685 (Alito, J., concurring in the judgment) (implying that FDA inactions in light of "[its § 355(o)(4)(A)] duty arguably affect the pre-emption analysis").

More to the point, the FDA "communicate[s] with applicants about scientific, medical, and procedural issues that arise" when it reviews a request for regulatory action. 21 C.F.R. § 314.102(a). More specifically, § 314.110(a)(2) imposes a "complete description" requirement when the agency sends a CRL; § 355(o)(4)(A) imposes an "obligation to initiate a label change" if the FDA believes one is warranted; § 314.110(a)(3) states that a CRL reflects the "FDA's complete review of the data submitted," not merely the particular labeling language proposed; and under § 314.105(b), the FDA may approve an application with "minor deficiencies" contingent on appropriate corrections. Taken together, these provisions warrant the following inference as to the FDA's intention when it issued the CRL: the Agency did not believe there was reasonable scientific evidence of a causal association between bisphosphonate use and atypical femoral fractures, or else it would have suggested edits to that end, or simply mandated a warning using language that the FDA thought was more appropriate, similar to what the Agency ultimately did in 2010.

What is more, the FDA red-lined Defendant's proposed "stress fractures" language between October 2010, when the Agency imposed a label change, and January 2011, when Defendant implemented the Agency's Precautions warning as-written. Were such language the sole problem with the 2008 warning, then the FDA could have simply stricken it, as it did

two years later, or approved it on the condition that Defendant implement edits pursuant to 21 C.F.R. § 314.105(b). But, an issue existed in 2008 that did not exist in 2010, one that could not be resolved with any revisions: in 2008, the FDA was unconvinced of the causal link between bisphosphonate use and atypical femoral fractures. The Agency's contrasting approaches to Defendant's proposed "stress fractures" language cannot be reconciled otherwise. Accordingly, it follows from the regulatory regime that the FDA rejected Defendant's warning for lack of reasonable evidence of causation.

iii. *The Scope of the CRL*

Having determined the context of the CRL, I next determine the FDA's likely response to another proposed warning based on how it *did* respond in the CRL. *See, e.g., Fosamax*, 852 F.3d at 293 (stating that the preemption inquiry requires "pars[ing]" the FDA's actual response "to discern what it suggests about the FDA's likely response"); *Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264, 1277 (W.D. Ok. 2011) (finding preemption even though the FDA later determined that sufficient evidence existed to justify a warning, in part because it was "highly persuasive" that the FDA rejected a similar warning before).

1. A Revised PAS

Plaintiffs first argue that the FDA would have approved a differently worded Precautions warning had Defendant simply removed the "stress fractures" language and resubmitted its PAS. Pl. Br., at 29 ("FDA invited further action from [Defendant] on at least four occasions, over several months, in various formats

(email, formal letter, telephone call). Thus, 'the ball was back in [Defendant's] court to submit a revised, corrected proposal.'") (quoting *Fosamax*, 852 F.3d at 299).

Judge Pisano disagreed, finding that "the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning" in the CRL. *OTSC Opinion*, 2014 WL 1266944, at *16. Construed in light of the FDA's communications and the regulations governing prescription drug labeling, I also find that: the CRL denied Defendant's Precautions warning because the FDA doubted the causal connection, if any, between bisphosphonates and low-energy femur fractures, and to that extent, the letter foreclosed the possibility that the FDA would have approved a differently worded warning in a revised PAS, without any substantial change in science.

Plaintiffs' evidence to the contrary is unavailing. Indeed, while the FDA mentioned working with Defendant in April 2009 "to decide on language" for a warning in the Precautions section, the Agency conditioned that response with explicit language that only "if it [was] warranted," an important qualification signaling the uncertain state of the underlying science. In fact, in the same email, the FDA instructed Defendant to "hold off" on a Precautions warning, which was "prolonging review," so that it could "close out" its PAS and "agree quickly" to changes in the Adverse Reactions section, another sign that the Agency was not prepared to approve any revised Precautions language.

Plaintiffs also point to various interactions between May and July 2009, purporting to show that Defendant declined to engage with the FDA *after* the CRL was issued. Pl. Br., at 28-29. Each interaction, put into context, however, is an *attempt* by Defendant to *initiate* further discussion, which *the Agency* rebuffed. For instance, in a June 2009 phone call, Defendant asked for "a teleconference" to discuss revisions to its Precautions warning. Pl. Br., Ex. 13 ("I asked . . . would the Division be open to a teleconference to discuss what may be acceptable."). But the FDA responded that Defendant must "formally" request one. *Id.* ("[The FDA official] replied such requests should be made formally through a submission to the file.").

Soon thereafter, by email, Defendant reiterated its desire to discuss a Precautions warning. *Id.*, Ex. 14 ("Per your recommendation from a previous conversation this [potential] meeting would be requested formally as a Type C meeting."). Days later, however, the FDA informed Defendant in another phone call that it must "address *both* issues highlighted in the [CRL] to initiate a new review cycle . . . or . . . withdraw the previous PAS." *Id.*, Ex. 15 (emphasis added); 21 C.F.R. § 314.110(b) (requiring a drug manufacturer to "address[] all deficiencies identified" by the FDA if it chooses to resubmit its application). One issue was the "inadequate justification" for the warning, which embodied the FDA's then-existing skepticism on causation. Defendant received the same response when it asked the Agency to keep its PAS open pending further discussion.

Likewise, in its Adverse Reactions CBE amendment in July 2009, Defendant stated that it "still believe[d]" in a Precautions warning about "low-energy fracture[s]" and anticipated requesting a formal meeting on that issue per the FDA's prior instructions. *Id*., Ex. 16. Defendant never did so, and Plaintiffs demand an adverse inference for it. But, Plaintiffs overlook the fact that withdrawal is a lawful response to a CRL. 21 U.S.C. § 314.70(c)(6)(iii)(A). Moreover, a formal meeting is not a prerequisite to preemption. *Dolin*, 901 F.3d at 814 (rejecting plaintiff's argument that defendant's failure to request a formal meeting with the FDA after receiving a CRL barred preemption, which "misunderstands the preemption standard"); *see also PLIVA*, 564 U.S. at 619-20 (rejecting plaintiff's argument that defendant's failure to ask the FDA to change the brand-name label barred preemption for a generic manufacturer, because what matters is that the manufacturer "cannot independently satisfy its state duties without the Federal Government's special permission and assistance").

Plaintiffs' argument is essentially that Defendant *could have, perhaps, theoretically*, changed the FDA's decision had Defendant somehow insisted on engaging with the Agency or invoked an available procedural mechanism rather than withdraw its PAS, but "the possibility of [that] possibility" is certainly not enough to "defeat[] pre-emption." *PLIVA*, 564 U.S. at 626 n.8; *cf. In re Actos (Pioglitazone) Prod. Liab. Litig.*, No. 11-2299, 2014 WL 4364832, at *20 (W.D. La. Sept. 2, 2014) (rejecting manufacturer's preemption defense because of substantial evidence that the manufacturer declined various FDA efforts to require a stronger

warning); *Dorsett v. Sandoz*, Inc., 699 F. Supp. 2d 1142, 1159 (S.D. Cal. 2010) ("Defendants offer nothing but theoretical assumptions of what the FDA would have done, and that is not enough to warrant a finding of preemption."). Indeed, Plaintiffs have presented no evidence that the FDA made any suggestions, at the time it issued the CRL, that it would somehow change its decision regarding the proposed warning if Defendant made certain changes. Rather, the Agency rejected the warning based on a lack of scientific evidence, and it follows that the FDA would not have approved a Precautions warning had Defendant simply omitted the "stress fractures" language and resubmitted its PAS.

2. *A CBE Amendment*

Plaintiffs also suggest that Defendant, on its own initiative, could have amended the Precautions section of the Fosamax label through a CBE amendment. The CBE process permits a drug manufacturer to unilaterally add a Precautions warning to its label, but only if "newly acquired information" provides "reasonable evidence of a causal association of a clinically significant adverse reaction linked to a drug." 21 C.F.R. §§ 314.70(c)(6)(iii), 201.57(c)(6)(i). The question of whether newly acquired information exists is fact-intensive, but because it is "part and parcel of the broader legal [preemption] question," *Merck*, 139 S.Ct. at 1680, it is incumbent upon this Court to decide. *Lyons v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 2020 WL 5835125, at *8 (N.D. Ga. Sept. 29, 2020) (collecting cases holding same).

"Newly acquired information" can take many forms. Information previously known to a manufacturer, but

not submitted to the FDA, may suffice,73 Fed. Reg. at 49,606, as well as "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*." *Wyeth*, 555 U.S. at 569 (emphasis added); 21 C.F.R. § 314.3(b). This "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Wyeth*, 555 U.S. at 569. Notably, however, the CBE process does not exempt the proposed change from the FDA's substantive requirements, nor does it eliminate FDA jurisdiction—two points that Plaintiffs acknowledge. Indeed, the FDA retains authority to review amendments submitted through the CBE process, and it will *reject* a CBE amendment if, among other things, it concludes that there is insufficient evidence of a link between the drug and the adverse event or the proposed change "requires approval prior to distribution." 73 Fed. Reg. 2848, 2851; 21 C.F.R. 314.70(c)(5)(i); *see also id*. 314.70(c)(7) ("If the agency disapproves the [CBE], it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change."); 71 Fed. Reg. 3922, 3934 ("FDA reviews all such submissions and may later deny approval of" a CBE; "[t]hus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling"). Case law also highlights this important characteristic of the CBE process. *See Wyeth*, 555 U.S. at 571 ("Of course, the FDA retains authority to reject labeling changes made pursuant to the CBE

regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications."); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) ("It is technically a violation of federal law to propose a CBE that is not based on reasonable evidence.").

Here, as of March 2010, the fact that the FDA still believed that "reasonable evidence of a causal association" was lacking and that it rejected Merck's proposed Precaution in 2009, demonstrate that it would not have approved the same change by way of a CBE amendment. *See Dobbs*, 797 F. Supp. 2d at 1276 (noting that the FDA had rejected risk information added by a CBE amendment because "it did not believe that a causal association" between the drug and the purported risk "has as yet been definitively established"). Indeed, as a matter of procedure, in order for Defendant to proceed with the CBE process after the FDA rejected its PAS—Merck was required to produce data indicating a greater-than-previously-known risk of atypical femoral fractures, which could establish "reasonable evidence" of a causal association. *Drescher v. Bracco Diagnostics, Inc.*, 2020 WL 699878, at *4 (D. Az. Jan. 31, 2020) (examining "whether Plaintiff has pled reasonable evidence of a causal association sufficient to allow a CBE label change"); *Dobbs*, 797 F. Supp. 2d at 1272 ("The FDA has consistently defined reasonable evidence . . . as 'when evidence exists on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug.'"); 44 Fed. Reg. 2848, 2851 (allowing a CBE amendment only for "known hazards

and not theoretical possibility"); *id*. at 49,604 (stating that this is how the FDA ensures "scientifically accurate information appears in the approved labeling"); *see also Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 707 (2d Cir. 2019) (holding that manufacturers are "limited in their ability to unilaterally change the labels on their products" because they must comply with the CBE regulation's causation thresholds); *Merck*, 139 S.Ct. at 1677 (explaining that, "when the risks of a particular drug become *apparent*, the manufacturer has a duty to provide a warning that adequately describes the risk") (emphasis added).

Certainly, no additional data between the period of time when the FDA issued its CRL and when the Agency finally decided to issue a Precautions warning, "reveal[ed] risks of a different type or greater severity or frequency" than the ones which Defendant knew, informed the FDA, and sought to warn against in the first instance. 21 C.F.R. § 314.3(b). Defendant submitted its PAS in September 2008, concluding based on the research at the time that "[i]t is not possible with the present data to establish whether" Fosamax "increases the risk of . . . low-energy subtrochanteric and/or proximal shaft fractures." Pl. Br., Ex. 38, A1349. And, while Plaintiffs point to certain unidentified and unspecified case studies and articles, which purportedly demonstrate a different risk profile for Fosamax with respect to atypical femoral fractures that were available to Defendant between submission of its PAS in September 2008 and the Task Force Report in October 2010, those case studies and articles have neither been provided to the Court, nor summarized. Thus, the Court cannot

evaluate the conclusions reached by those articles and case studies, nor can it even definitively determine whether Merck ever independently reviewed or provided those materials to the FDA.

Moreover, even if those articles and case studies existed, in March 2010, the FDA announced that it had not seen "a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures," "an increase in the risk in women using [bisphosphonates]," or "[different] numbers of atypical subtrochanteric femur fractures" in "patients taking bisphosphonates" versus patients "not taking bisphosphonates" after reviewing case reports and clinical trial data from *all* bisphosphonate drug manufacturers. Pl. Br., Ex. 18, at A1508. These conclusions mirror those in Defendant's PAS, and to that extent, do not shed light on any "newly acquired information" in the sense of the CBE regulation. In other words, even though the FDA's then-ongoing review was arguably *more thorough* than any review it might have conducted under the CBE process—the Agency was compiling data from multiple manufacturers, analyzing a variety of new reports, revisiting old ones, conducting its own analyses, and working with outside experts on the Task Force—it did not uncover definitive evidence linking Fosamax use to atypical femoral fractures to a greater extent than Defendant originally indicated.

Then, in September 2010, the Task Force published its Report, which developed a "provisional case definition" for the "features for complete and incomplete atypical [femoral] fractures," reassessed prior studies in light of that definition, and reviewed a number of new articles/reports that Defendant had not

previously submitted to the FDA, but added nothing not already known. Shane et al., at 2267-69. Still, according to the Report, "a causal association between [bisphosphonates] and atypical fractures ha[d] not been established." *Id*. The science merely supported "evidence of a *relationship* between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture." Pl. Br., Ex. 2, at A1167 (emphasis added). Defendant and the FDA, alike, had long recognized the same. *See, e.g*., Pl. Br., Ex. 10, at A1145 (stating, in June 2008, that the Agency was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates," that these were "reportedly rare in patients with osteoporosis not on bisphosphonates," and that it was "concerned about this developing safety signal"); *Fosamax*, 852 F.3d at 275 (citing A1258) (forwarding an article stating that Fosamax "may . . . potentially" increase the risk of such fractures); *id*. (citing A1237) (forwarding an article stating that Fosamax "may be associated" with such fractures"); *id*. (citing A1243) (forwarding an article stating that certain findings "raise[d] the possibility" that Fosamax may lead to such fractures).

Given the conclusions in the Task Force Report, there was no "newly acquired information" as defined in the CBE regulation on the basis of which Defendant could have successfully submitted a CBE amendment. *Accord In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Prod. Liab. Litig.*, 185 F. Supp. 3d 761, 769 (D.S.C. 2016) (holding that a drug label cannot be changed based solely on "information previously submitted to the FDA"); *Dolin*, 901 F.3d at 816 ("The [2011] article contained the same figures as

GSK's 2006 analysis, which GSK submitted to the FDA. There is no basis to conclude that this was a new analysis or that it was 'not previously submitted to the Agency.'"); *Knight*, 984 F.3d at 339 (explaining how a new article showing a "correlation" is insufficient to defeat preemption because the FDA already knew that); *In re Incretin*, 142 F. Supp. 3d at 1123 (stating that "indeterminate" or "inconclusive" evidence is not "reasonable evidence" sufficient to justify a CBE amendment); *Seufert*, 187 F. Supp. 3d at 1175 (stating that a CBE amendment "demands more than an indeterminate or inconclusive relationship"); *McGrath*, 393 F. Supp. 3d at 168 ("For the Court to draw the reasonable inference that Bayer could have unilaterally amended the Magnevist label in compliance with the FDA's CBE regulation, the Complaint must plead more than the mere possibility that Magnevist caused Plaintiff's fibrosis and related injuries."). The "new" evidence published after Defendant submitted its PAS, and relied upon by Plaintiffs, established the very relationship or connection Defendant had identified all along.[20]

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[20] The Task Force Report also "suggest[ed] that the risk rises with increasing duration of exposure." *Id*. But this was not new information to the FDA either. Pl. Br., Ex. 2, at A1147 ("The duration of [bisphosphonate use] relative to onset of the fracture was 5.3 years mean and 5 years median with a range from 3 months to 14 years."); *Merck*, 139 S.Ct. at 1674 (describing a report from a doctor in 2002 stating that his hospital called atypical femoral fractures the "Fosamax Fracture" because "100% of patients in his practice who have experienced femoral fractures . . . were taking Fosamax . . . *for over 5 years*") (emphasis added); *Merck*, 139 S.Ct. at 1674 ("[Defendant began receiving adverse event reports from the medical community indicating that *long-term Fosamax users* were suffering atypical

The FDA responded to the Task Force by issuing another Drug Safety Announcement in September 2010, but with the same conclusion as before: the Report would "facilitate future studies" assessing a causal link between "these unusual femur fractures" and bisphosphonate use, but "it is not clear if bisphosphonates are the cause [of such fractures]." Def. Br., Ex. 9, at A1512. This, too, echoes Defendant's original assessment of the science/evidence and implies no new risks or correlations of which the FDA was not already aware. *McGrath*, 2019 WL 2582530, at *5 ("Studies concluding it 'remains unknown whether GBCAs induce toxic effects' and that 'further studies are required to address possible clinical consequences of gadolinium deposition . . . in patients with normal renal function' do not constitute reasonable or well-grounded scientific evidence of 'clinically significant adverse effects' under the CBE regulation."); *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 669 (S.D.N.Y. 2017) (same, but with respect to articles that "merely express a desire for further investigation"), *aff'd sub nom. Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019).

Finally, in October 2010, the FDA mandated a change to the Fosamax label, yet *again* it rejected any causal link, which is "squarely in line" with its prior conclusions and Defendant's ongoing dialogue with the Agency. *Lyons*, 491 F. Supp. 3d at 1364. The Task Force Report merely made the FDA "confident" that

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femoral fractures.") (emphasis added); *Fosamax*, 852 F.3d at 275 (citing A1258, A1237, A1243) (describing how Defendant "began to see numerous scholarly articles and case studies documenting possible connections between *long-term Fosamax use* and atypical femoral fractures") (emphasis added).

atypical femur fractures are "potentially more *closely related* to" long-term use of bisphosphonates "than [the Agency] previously had evidence for." Def. Br., Ex. 6, at A1392-93 (emphasis added). The now-current Fosamax label, as written by the FDA, refuses to go any further than Defendant's proposal thirteen years ago: "Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates." *Accord Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 44 (2011) ("The fact that a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event.").

In any event, the FDA's review of Defendant's CBE amendment would not have been any less rigorous than its review of Defendant's PAS, particularly since the FDA was conducting its own review of causation at the time when Defendant had the opportunity to submit a CBE amendment, and Defendant's view of the scientific evidence would not have been entitled to extra (or any) deference. *Accord In re Incretin*, 142 F. Supp. 3d at 1125. In fact, drug manufacturers almost always consult with the FDA before submitting CBE amendments to avoid future enforcement action for an unwarranted warning. *Id.* There was much correspondence between the FDA and Defendant here, none of which indicated that the Agency would permit Defendant to implement a Precautions warning through the CBE process, but not through the PAS process. In fact, and importantly, the FDA suggested that Defendant submit a label change for the Adverse Reactions section through the CBE process, but it did not make the same recommendation for the Precautions warning. Based on these FDA

communications, it is difficult to imagine that Defendant could have successfully changed the Fosamax label through the CBE regulation after the FDA rejected its PAS.

Contrary to Plaintiffs' position, while Defendant of course could have *tried* to submit a CBE amendment, regardless of futility, *Merck*, 139 S.Ct. at 1975; Pl. Br., Ex. 17, at T181:23-182:12, it need not do so merely to preserve its preemption defense. A manufacturer is under no obligation to use the CBE process to change the Precautions section of its label for any reason other than reasonable evidence of a causal association. *Wyeth*, 555 U.S. at 571 (cautioning that the mere availability of a CBE amendment does not defeat preemption); *PLIVA*, 564 U.S. at 628 n.8 (noting that "the possibility of possibility" is not enough); *Dolin*, 951 F.3d at 890-91 (explaining how the phrase "would not have approved" in *Wyeth* implies that a drug manufacturer may prove preemption without showing that it ever attempted to make a label change); *Cerveny*, 783 Fed. App'x. at 804 n.8 (rejecting notion that "only labeling changes sought by the manufacturer can lead to preemption"); *Cerveny*, 155 F. Supp. 3d at 1213-16 (explaining that lower courts have "universally rejected" the notion "that [*Wyeth*] requires a showing that the manufacturer attempted to apply the warning suggested by the plaintiff but that the labeling was ultimately rejected by the FDA"); *In re Incretin*, 142 F. Supp. 3d at 1126 ("[*Wyeth*] does not require CBE submission and rejection."); *Zofran*, 2021 WL 2209871, at *32 ("Multiple courts have found preemption where the manufacturer had not requested the precise warning sought by the plaintiffs

when the FDA had nonetheless made it clear that it would not accept that label change.").

A contrary rule would incentivize manufacturers to submit a CBE amendment regardless of risk magnitude or scientific justification, which would impose an undue burden on the FDA. *Wyeth*, 555 U.S. at 578-79 & n.11 ("[The] FDA has limited resources to monitor the 11,000 drugs on the market."); *Seufert*, 187 F. Supp. 3d at 1175 ("A rule to the contrary would encourage prophylactic labeling changes by manufacturers, which, in turn, could inundate the FDA with labeling submissions."); FDA, *FDAAA Implementation – Highlights Two Years After Enactment* 7 (2010) (finding just 363 CBE amendments between 2009 and 2010). Not to mention that "[i]t is technically a violation of federal law to propose a CBE that is not based on reasonable evidence." *Mason*, 596 F.3d at 392; *Drescher*, 2020 WL 699878, at *4 (concluding same).

Moreover, the FDA does not approve CBE amendments simply out of an abundance of caution, as Plaintiffs seem to suggest. The Agency regulates drug labels for precisely the opposite reason: so as not to "cause meaningful risk information to lose its significance." 73 Fed. Reg. 2848, 2851 ("Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug . . . or decrease the usefulness and accessibility of important information by diluting or obscuring it."). Indeed, "[w]hile it is important for a manufacturer to warn of potential side effects, it is equally important that it not overwarn because overwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted and can dilute the

effectiveness of valid warnings." *Mason*, 596 F.3d at 392. The FDA is thus appropriately wary of "the resulting information overload [which] would make label warnings worthless to consumers." *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 870-71 (7th Cir. 2010); *Muzichuck v. Forest Laboratories*, 2015 WL 235226, at *7 n.2 (N.D.W.V. Jan. 16, 2015) ("Public policy recognizes a danger in 'overwarning' consumers of potential drug-related risks."). Accordingly, Defendant could not have met the relevant CBE criteria had it submitted a Precautions warning through that regulation after the FDA rejected its PAS.

CONCLUSION

Based on clear and convincing evidence, the Court finds that Defendant fully informed the FDA of the justifications for its proposed warning, which was adequate under state law and encompassed the injury Plaintiffs allege here. The FDA, in turn, informed Defendant that it would not approve changing the Fosamax label to include that warning in the CRL. Because the basis for the FDA's rejection was insufficient evidence of a causal link between Fosamax and atypical femoral fractures, the Court is satisfied that the evidence is clear and convincing that the Agency would not have approved a differently worded warning no matter how Defendant attempted to submit one. Plaintiffs' state law failure-to-warn claims are therefore preempted, and Defendant's Motion for Summary Judgment is **GRANTED**.

DATED: March 23, 2022 /s/ Freda L. Wolfson
Hon. Freda L. Wolfson
U.S. Chief District Judge

APPENDIX C

UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 22-3412

In re: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION

Phyllis Molnar and all other plaintiffs listed in Exhibit A to notice of appeal,

Appellants

On Appeal from the United States District Court
For the District of New Jersey
(D.C. No. 3-08-cv-00008)
District Judge: Honorable Freda L. Wolfson

SUR PETITION FOR PANEL REHEARING

Case: 22-3412 | Document: 89 | Date Filed: 11/19/2024

Present: JORDAN, PHIPPS, and FREEMAN, *Circuit Judges*

The Petition for Panel Rehearing having been submitted to the judges who participated in the decision of this Court, and the Petition having been duly considered, it is hereby ORDERED that the Petition is DENIED.

BY THE COURT,

s/ Kent A. Jordan
Circuit Judge

Dated: November 19, 2024

CJG/cc: David C. Frederick, Esq.
Ariela Migdal, Esq.
James Ruck, Esq.
Mark Sparks, Esq.
John R. Boule, Esq.
Karen A. Confoy, Esq.
Jeffrey J. Johnson, Esq.
Stephen E. Marshall, Esq.
Eileen O. Muskett, Esq.
Jacob M. Roth, Esq.
William B. Schultz, Esq.
Robert S. Peck, Esq.
Kevin M. Gallagher, Esq.
Elizabeth J. Cabraser, Esq.
Avery S. Halfon, Esq.
Andrew R. Kaufman, Esq.
Ernest A. Young, Esq.

APPENDIX D

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21 U.S.C. § 355

§ 355. New drugs

* * *

(b) Filing application; contents

(1)(A) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application--

(i) full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use;

(ii) a full list of the articles used as components of such drug;

(iii) a full statement of the composition of such drug;

(iv) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(v) such samples of such drug and of the articles used as components thereof as the Secretary may require;

(vi) specimens of the labeling proposed to be used for such drug;

(vii) any assessments required under section 355c of this title; and

(viii) the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that--

(I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or

(II) claims a method of using such drug for which approval is sought or has been granted in the application.

(B) If an application is filed under this subsection for a drug, and a patent of the type described in subparagraph (A)(viii) is issued after the filing date but before approval of the application, the applicant shall amend the application to include the patent number and expiration date.

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include--

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which

information is required to be filed under paragraph (1) or subsection (c)--

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed

(A) Agreement to give notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph--

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice

An applicant required under this paragraph to give notice shall give notice to--

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice

A notice required under this paragraph shall--

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug

before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of Title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of Title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size--

(i)(I) of clinical trials intended to form the primary basis of an effectiveness claim; or

(II) in the case where human efficacy studies are not ethical or feasible, of animal and any associated clinical trials which, in combination, are intended to form the primary basis of an effectiveness claim; or

(ii) with respect to an application for approval of a biological product under section 262(k) of Title 42, of any necessary clinical study or studies.

The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity

for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of Title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 282(j)(5)(B) of Title 42. Such certification shall not be considered an element of such application.

* * *

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said

subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this

subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

* * *

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug

involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

(2) Definitions

For purposes of this subsection:

(A) Responsible person

The term "responsible person" means a person who--

(i) has submitted to the Secretary a covered application that is pending; or

(ii) is the holder of an approved covered application.

(B) Covered application

The term "covered application" means--

(i) an application under subsection (b) for a drug that is subject to section 353(b) of this title; and

(ii) an application under section 262 of Title 42.

(C) New safety information; serious risk

The terms "new safety information", "serious risk", and "signal of a serious risk" have the meanings given such terms in section 355-1(b) of this title.

(3) Studies and clinical trials

(A) In general

For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including

information regarding chemically-related or pharmacologically-related drugs.

(B) Purposes of study or clinical trial

The purposes referred to in this subparagraph with respect to a postapproval study or postapproval clinical trial are the following:

(i) To assess a known serious risk related to the use of the drug involved.

(ii) To assess signals of serious risk related to the use of the drug.

(iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

(C) Establishment of requirement after approval of covered application

The Secretary may require a postapproval study or studies or postapproval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.

(D) Determination by Secretary

(i) Postapproval studies

The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).

(ii) Postapproval clinical trials

The Secretary may not require the responsible person to conduct a clinical trial under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).

(E) Notification; timetables; periodic reports

(i) Notification

The Secretary shall notify the responsible person regarding a requirement under this paragraph to conduct a postapproval study or clinical trial by the target dates for communication of feedback from the review team to the responsible person regarding proposed labeling and postmarketing study commitments as set forth in the letters described in section 101(c) of the Food and Drug Administration Amendments Act of 2007.

(ii) Timetable; periodic reports

For each study or clinical trial required to be conducted under this paragraph, the Secretary shall require that the responsible person submit a timetable for completion of the study or clinical trial. With respect to each study required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such study including whether any difficulties in completing the study have been encountered. With respect to each clinical trial required to be conducted under this paragraph or otherwise undertaken by the

responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such clinical trial including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to the requirements under section 282(j) of Title 42. If the responsible person fails to comply with such timetable or violates any other requirement of this subparagraph, the responsible person shall be considered in violation of this subsection, unless the responsible person demonstrates good cause for such noncompliance or such other violation. The Secretary shall determine what constitutes good cause under the preceding sentence.

(F) Dispute resolution

The responsible person may appeal a requirement to conduct a study or clinical trial under this paragraph using dispute resolution procedures established by the Secretary in regulation and guidance.

(4) Safety labeling changes requested by Secretary

(A) New safety or new effectiveness information

If the Secretary becomes aware of new information, including any new safety information or information related to reduced effectiveness, that the Secretary determines should be included in the

labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) shall within 30 days--

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions, or new effectiveness information; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety or new effectiveness

information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) to make such a labeling change as the Secretary deems appropriate to address the new safety or new effectiveness information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

(G) Violation

If the responsible person or the holder of the approved application under subsection (j) has not submitted a supplement within 15 days of the date of such order under subparagraph (E), and there is

no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) Public health threat

Notwithstanding subparagraphs (A) through (F), if the Secretary concludes that such a labeling change is necessary to protect the public health, the Secretary may accelerate the timelines in such subparagraphs.

(I) Rule of construction

This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under subsection (j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations).

(5) Non-delegation

Determinations by the Secretary under this subsection for a drug shall be made by individuals at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research).

* * *

21 C.F.R. § 201.57

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

* * *

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

(1) Highlights limitation statement. The verbatim statement "These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)."

(2) Drug names, dosage form, route of administration, and controlled substance symbol. The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04 of this chapter.

(3) Initial U.S. approval. The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on

the line immediately beneath the established name or, for biological products, proper name of the product.

(4) Boxed warning. A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."

(5) Recent major changes. A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))"

(7) Dosage and administration. A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) Dosage forms and strengths. A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any

appropriate subheadings, including 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.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) Drug interactions. A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) Use in specific populations. A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) Patient counseling information statement. The verbatim statement "See 17 for Patient Counseling Information" or, if the product has FDA-approved patient labeling, the verbatim statement "See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide)."

(15) Revision date. The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

* * *

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that

includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) 1 Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) 2 Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active

ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

(4) 3 Dosage forms and strengths. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) 4 Contraindications. This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other

condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state "None."

(6) 5 Warnings and precautions.

(i) General. This section 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 or those resulting from drug/drug interactions), limitations in 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. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease

or condition and such usage is associated with a clinically significant risk or hazard.

(ii) Other special care precautions. This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) Monitoring: Laboratory tests. This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) Interference with laboratory tests. This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) 6 Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) Listing of adverse reactions. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100,

adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) Postmarketing experience. This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) Comparisons of adverse reactions between drugs. For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(8) 7 Drug interactions.

(i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The

mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.

(ii) This section must also contain practical guidance on known interference of the drug with laboratory tests.

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21 C.F.R. § 314.70

§ 314.70 Supplements and other changes to an approved NDA.

* * *

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made

using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

* * *

21 C.F.R. § 314.71

§ 314.71 Procedures for submission of a supplement to an approved application.

* * *

(b) All procedures and actions that apply to an application under § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements except as specified otherwise in this part.

21 C.F.R. § 314.102

§ 314.102 Communications between FDA and applicants.

(a) General principles. During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) Notification of easily correctable deficiencies. FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration

of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

* * *

21 C.F.R. § 314.105

§ 314.105 Approval of an NDA and an ANDA.

* * *

(b) FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

* * *

21 C.F.R. § 314.110

§ 314.110 Complete response letter to the applicant.

(a) Complete response letter. FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(1) Description of specific deficiencies. A complete response letter will describe all of the specific deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

(2) Complete review of data. A complete response letter reflects FDA's complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments that the agency has reviewed. The complete response letter will identify any amendments that the agency has not yet reviewed.

(3) Inadequate data. If FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.

(4) Recommendation of actions for approval. When possible, a complete response letter will recommend actions that the applicant might take to

place the application or abbreviated application in condition for approval.

(b) Applicant actions. After receiving a complete response letter, the applicant must take one of following actions:

(1) Resubmission. Resubmit the application or abbreviated application, addressing all deficiencies identified in the complete response letter.

(i) A resubmission of an application or efficacy supplement that FDA classifies as a Class 1 resubmission constitutes an agreement by the applicant to start a new 2–month review cycle beginning on the date FDA receives the resubmission.

(ii) A resubmission of an application or efficacy supplement that FDA classifies as a Class 2 resubmission constitutes an agreement by the applicant to start a new 6–month review cycle beginning on the date FDA receives the resubmission.

(iii) A resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new review cycle the same length as the initial review cycle for the supplement (excluding any extension due to a major amendment of the initial supplement), beginning on the date FDA receives the resubmission.

(iv) A major resubmission of an abbreviated application constitutes an agreement by the applicant to start a new 6–month review cycle beginning on the date FDA receives the resubmission.

(v) A minor resubmission of an abbreviated application constitutes an agreement by the applicant

to start a new review cycle beginning on the date FDA receives the resubmission.

(2) Withdrawal. Withdraw the application or abbreviated application. A decision to withdraw an application or abbreviated application is without prejudice to a subsequent submission.

(3) Request opportunity for hearing. Ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively. The applicant must submit the request to the Associate Director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993. Within 60 days of the date of the request for an opportunity for a hearing, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated application under § 314.105, or refuse to approve the application under § 314.125 or abbreviated application under § 314.127 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(1)(B) or (j)(5)(c) of the act on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively.

* * *

APPENDIX E

Exhibit A

Plaintiff Name	Case Name	Case No.
Molnar, Phyllis	Molnar, Phyllis	08-cv-8
Gozdziak, Margaret	Gozdziak, Margaret	09-cv-5630
Duke, Dolores	Duke, Dolores	09-cv-5693
Schultz, Susan S.	Schultz, Susan	10-cv-3545
Hines, Cynthia H.	Hines, Cynthia	10-cv-4839
Goodwin, Joan H.	Goodwin, Joan	10-cv-5461
Moline, Barbara R.	Moline, Barbara	10-cv-5462
Lamirande, Louella	Lamirande, Louella	10-cv-6049
Wheeler, Kathryn K.	Wheeler, Kathryn	10-cv-6282
Metz, Theresa	Metz, Theresa	11-cv-1286
Kolb, Lauren	Kolb, Lauren	11-cv-1498
Dematto, Mary E.	Dematto, Mary	11-cv-1886
Homler, Shirley	Homler, Shirley	11-cv-3162

Plaintiff Name	Case Name	Case No.
Germino, Virginia Lee	Germino, Virginia Lee	11-cv-3165
Chaires, Jeanette S.	Chaires, Jeanette	11-cv-3168
Salvatore, Sheila	Salvatore, Sheila	11-cv-3169
Collins, Lucille	Collins, Lucille	11-cv-3170
Young, Marilyn	Young, Marilyn	11-cv-3225
Denker, Elayne	Denker, Elayne	11-cv-33
Sunshine, Beverly	Sunshine, Beverly	11-cv-3309
Sutton, Barbara	Sutton, Barbara	11-cv-3310
Davis, Judith	Davis, Judith	11-cv-3313
Wolowick, Nancy Antoinette	Goodman, Arlene	11-cv-3320
Nelson, Ethelinda	Nelson, Ethelinda	11-cv-3367
Granato, Irene A.	Granato, Irene	11-cv-3369
Jeffries, Marilyn	Jeffries, Marilyn	11-cv-3370
Graves, Barbara	Graves, Barbara	11-cv-3645
Brown, Elizabeth	Brown, Elizabeth	11-cv-3867
Van, Mary Evelyn	Van, Mary Evelyn	11-cv-3911
Lapan, Evelyn	Lapan, Evelyn	11-cv-3912

Plaintiff Name	Case Name	Case No.
Zessin, Deloris M.	Zessin, Deloris	11-cv-3919
Wirth, Carol	Wirth, Carol	11-cv-3930
Naccio, Josephine P.	Naccio, Josephine	11-cv-4055
Foley, Peggy	Foley, Peggy	11-cv-4171
O'Brien, Molly (aka Mary)	O'Brien, Molly	11-cv-4242
Evans, Laura	Evans, Laura	11-cv-4277
Warner, Sharon	Warner, Sharon	11-cv-4955
Cortez, Lorice	Cortez, Lorice	11-cv-5025
Hardy, Shirley	Hardy, Shirley	11-cv-5077
Marks, Martha	Marks, Martha	11-cv-5079
Murphy, Nancy	Murphy, Nancy	11-cv-5082
Grassucci, Shirley	Grassucci, Shirley	11-cv-5083
Kahn, Sandra	Kahn, Sandra	11-cv-5150
Nakamura, Reiko	Nakamura, Reiko	11-cv-5297
Edwards, Sybil	Edwards, Sybil	11-cv-5300
Johnson, Susan	Johnson, Susan	11-cv-5301
Onaka, Eleanor	Onaka, Eleanor	11-cv-5302
Scott, Sylvia	Scott, Sylvia	11-cv-5303
Whitt, Betty Jean	Whitt, Betty Jean	11-cv-5335
Frampton, Barbara	Frampton, Barbara	11-cv-5564

Plaintiff Name	Case Name	Case No.
Heaton, Nancy	Heaton, Nancy	11-cv-570
Penigian, Jean	Penigian, Jean	11-cv-5703
Bonne, Virginia	Bonne, Virginia	11-cv-571
Squires, Kathryn	Berlin, Ruth	11-cv-5720
Collins, Joann	Collins, Joann	11-cv-5826
Lefebvre, Alice	Lefebvre, Alice	11-cv-586
Hogan, Marie	Hogan, Marie	11-cv-587
Karch, Lillie	Karch, Lillie	11-cv-589
Brogna, Loretta	Brogna, Loretta	11-cv-5912
Hodge, Helen	Hodge, Helen	11-cv-6162
Stark, Vivian	Stark, Vivian	11-cv-6164
Williams, Jerrie	Williams, Jerrie	11-cv-6244
Voss, Betty	Voss, Betty	11-cv-6347
McEwen, Karen	Schornick, Lori (PR-Karen McEwen Estate)	11-cv-6387
Panouis, Androniki	Panouis, Androniki	11-cv-6411
Blackford, June	Blackford, June	11-cv-6415
Krakovitz, Pearl	Krakovitz, Pearl	11-cv-6417
Pisarz, Josephine	Pisarz, Josephine	11-cv-6419
Strominger, Betty	Strominger, Betty	11-cv-6420
Schick, Joan	Schick, Joan	11-cv-6421

Plaintiff Name	Case Name	Case No.
Chee, Paula	Chee, Paula	11-cv-6451
Gribben, Angela	Gribben, Angela	11-cv-6452
Ourecky, Roberta	Ourecky, Roberta	11-cv-6468
Price, Carolyn	Price, Carolyn	11-cv-6469
White, Mary Belle	White, Mary Belle	11-cv-6478
Hoover, Jane	Hoover, Jane	11-cv-6650
Howe, Elaine	Howe, Elaine	11-cv-6657
Care, Margaret	Care, Margaret	11-cv-6694
Nelson, Gilda	Nelson, Gilda	11-cv-6695
Breeden, Judy	Breeden, Judy	11-cv-6749
Hanel, Kannika	Hanel, Kannika	11-cv-6817
Torregrossa, Ann M.	Torregrossa, Ann	11-cv-6874
Standish, Debbie	Standish, Debbie	11-cv-6912
Marcy, Ellen	Marcy, Ellen	11-cv-6922
Wilkins, Edith	Wilkins, Edith	11-cv-6945
Covey, Janet Stetler	Covey, Janet	11-cv-6946
Radford, Shirley	Radford, Shirley	11-cv-6947
Poynor, Sherry	Poynor, Sherry	11-cv-6948
Johnson, Janet	Johnson, Janet	11-cv-6959
Sontag, Marian	Sontag, Marian	11-cv-6983
Nelson, Edward	Nelson, Edward	11-cv-7020
Gordon, Sandra	Gordon, Sandra	11-cv-7022

Plaintiff Name	Case Name	Case No.
Haviland, Barbara	Haviland, Barbara	11-cv-7104
Shackelford, Margaret	Shackelford, Margaret	11-cv-7106
Matney, Rosemary	Matney, Rosemary	11-cv-7145
McGill, Barbara	McGill, Barbara	11-cv-7185
Morgan, Christine	Rose, Casey (PR-Christine Morgan Estate)	11-cv-7186
Schwalbe, Linda	Schwalbe, Linda	11-cv-7208
Goldklang, Charlotte	Goldklang, Charlotte	11-cv-7279
Nation, Karleen	Nation, Karleen	11-cv-7345
Misner, Anita	Misner, Anita	11-cv-7401
Burke, Louise Findley	Burke, Louise	11-cv-7429
Borri, Janice M.	Borri, Janice	11-cv-7431
Carter-Morcomb, Patty	Carter-Morcomb, Patty	11-cv-7432
Messerli, Donna	Messerli, Donna	11-cv-7491
McKee, Eleanor	McKee, Eleanor	11-cv-7493
Mayes, Claudice	Mayes, Claudice	11-cv-7516
Joyce, Michael	Joyce, Michael	11-cv-7517
Hensley, Mary	Hensley, Mary	11-cv-7518
Degen, Patricia	Degen, Patricia	11-cv-7519
Mahan, Caroline	Mahan, Caroline	11-cv-7520

Plaintiff Name	Case Name	Case No.
Mistretta, Wilma	Mistretta, Wilma	11-cv-7521
Sorrentino, Theresa	Sorrentino, Theresa	11-cv-7522
Tucker, Assunta	Tucker, Assunta	11-cv-7523
Green, Mariella	Green, Mariella	11-cv-7524
Greenway, Ann P.	Greenway, Ann	11-cv-7525
Ivey, Jane	Ivey, Jane	11-cv-7557
Driver, Virginia	Driver, Virginia	11-cv-7558
Walraed, Susan	Walraed, Susan	11-cv-869
Goggin, Carol	Goggin, Carol	12-cv-1021
Drouet, Renee	Drouet, Renee	12-cv-1036
Stroh, Kerry A.	Stroh, Kerry	12-cv-1038
Plato, Ruth R.	Plato, Ruth	12-cv-1051
DeClue, Shirley	DeClue, Shirley	12-cv-1052
Vannoy, Doris A.	Vannoy, Doris	12-cv-1072
D'Angelo, Kimiko	D'Angelo, Kimiko	12-cv-1093
Hardy, Yvette	Hardy, Yvette	12-cv-1132
Lynn, Vivian	Lynn, Vivian	12-cv-1133
Gitter, Blossom	Gitter, Blossom	12-cv-1135
Clow, Edna	Clow, Edna	12-cv-1177
Lyons, Janet	Lyons, Janet	12-cv-1180
Fitzpatrick, Nora	Fitzpatrick, Nora	12-cv-1181

Plaintiff Name	Case Name	Case No.
Suehiro, Tokia	Suehiro, Tokia	12-cv-1185
Brown, Linton	Brown, Linton	12-cv-1186
Seims, Marcie	Seims, Marcie	12-cv-1187
Andrejasich, Anne	Andrejasich, Anne	12-cv-1200
Hillenburg, Wilma	Hillenburg, Wilma	12-cv-1202
Edwards, Sally	Edwards, Sally	12-cv-1203
Kakareka, Edith	Kakareka, Edith	12-cv-1204
Jones, Denman	Jones, Denman	12-cv-1205
Morris, Joyce H. Peterson	Morris, Joyce	12-cv-1220
Murphy, Cheryl	Murphy, Cheryl	12-cv-1221
Spires, Evelyn	Spires, Evelyn	12-cv-1222
Steves, Susan	Steves, Susan	12-cv-1275
Flynn, Wilma	Flynn, Wilma	12-cv-1279
Jeffries, Gail	Jeffries, Gail	12-cv-1322
Jepson, Norma M.	Jepson, Norma	12-cv-1326
Fifer, Ladonna	Fifer, Ladonna	12-cv-1327
Moore, Marlene	Moore, Marlene	12-cv-1328
Bryant, Sharon	Bryant, Sharon	12-cv-1329
Bishop, Rosemary	Bishop, Rosemary	12-cv-1344
Dharamsi, Kanta Manoj	Bishop, Rosemary	12-cv-1344

Plaintiff Name	Case Name	Case No.
Howe, Linda L.	Bishop, Rosemary	12-cv-1344
Kohler, Elinor	Bishop, Rosemary	12-cv-1344
Peterson, Pura Gonzales	Bishop, Rosemary	12-cv-1344
Andrews, Mary	Andrews, Mary	12-cv-1347
Burleson, Jacqueline R.	Burleson, Jacqueline	12-cv-1356
Yost, Marilyn P.	Yost, Marilyn	12-cv-1387
Richard-Amato, Patricia	Richard-Amato, Patricia	12-cv-1395
Murphy, Betty	Murphy, Betty	12-cv-14
Cross, Katherine	Cross, Katherine	12-cv-1410
Mejia, Teresita	Mejia, Teresita	12-cv-1449
Agrow, Rosalie N.	Agrow, Rosalie	12-cv-1450
Crook, Patricia	Crook, Patricia	12-cv-1468
Fulkerson, Maria	Fulkerson, Maria	12-cv-1469
Courville, Paula R.	Courville, Paula	12-cv-1476
Bielecky, Margaret	Bielecky, Margaret	12-cv-1484
Wright, Judith	Wright, Judith	12-cv-1487
Gaynor, Barbara	Gaynor, Barbara	12-cv-1492

Plaintiff Name	Case Name	Case No.
Neal, Thelma	Sutton, Catrinia (PR-Thelma Neal Estate)	12-cv-15
Stuive, Madeline	Stuive, Madeline	12-cv-1548
Hayes, Mavis	Hayes, Mavis	12-cv-1549
Hanson, Nelda	Hanson, Nelda	12-cv-1552
Matzenbacher, Norma	Matzenbacher, Norma	12-cv-1565
Stencler, Roxanna	Stencler, Roxanna	12-cv-1566
Lowell, Sarah	Lowell, Sarah	12-cv-1567
Collier, Marion	Collier, Marion	12-cv-1568
Waldrup, Roberta	Waldrup, Roberta	12-cv-1569
Duffy, Joan	Duffy, Joan	12-cv-16
Herbert, Paula	Herbert, Paula	12-cv-1635
Pappas, Mary	Pappas, Diane (PR-Mary Pappas Estate)	12-cv-168
Pinkney, Lani	Pinkney, Lani	12-cv-17
Bohn, Patricia M.	Bohn, Edward (Attorney in Fact-Patricia Bohn)	12-cv-1715
Lavache, Bernice	Lavache, Bernice	12-cv-1716
Gill, Mary Jo	Gill, Mary Jo	12-cv-1717

Plaintiff Name	Case Name	Case No.
Gallop, Martha Oliver Crawley	Gallop, Martha	12-cv-1718
Kazemi, Farideh	Kazemi, Farideh	12-cv-1719
Jackson, Margie	Jackson, Margie	12-cv-1750
Freay, Onnolee	Freay, Onnolee	12-cv-1754
Chase, Brenda	Chase, Brenda	12-cv-1786
Nagy, Norma	Nagy, Norma	12-cv-18
Merrell, Preston	Merrell, Preston	12-cv-1845
Jones, Alice	Jones, Alice	12-cv-1846
Fracaro, Fern Lee	Fracaro, Fern Lee	12-cv-1847
Forkel, Delia	Forkel, Delia	12-cv-1848
McKelvey, Elizabeth	McKelvey, Elizabeth	12-cv-1849
Keaser, Barbara	Keaser, Barbara	12-cv-1850
Brenner, Lois	Brenner, Lois	12-cv-1875
Azar, Bernice	Azar, Bernice	12-cv-1876
Richardson, Lee	Richardson, Lee	12-cv-19
Hubbard, Linda	Hubbard, Linda	12-cv-1967
Arnold, Doris	Arnold, Doris NJ MDL	12-cv-1975
Halligan, Carla	Halligan, Carla	12-cv-1996
Frei, Miryam	Frei, Miryam	12-cv-1997
Besser, Margaret	Besser, Deborah (PR-Margaret Besser Estate)	12-cv-1998

Plaintiff Name	Case Name	Case No.
Dandridge, Earlene	Dandridge, Earlene	12-cv-1999
Weissberger, Kathryn	Weissberger, Kathryn	12-cv-2000
Mejia, Teresita	Mejia, Teresita	12-cv-2001
Stone, Harriet	Stone, Harriet	12-cv-2002
Pustilnik, Jean	Pustilnik, Jean	12-cv-2048
Skinner, Leone	Skinner, Leone	12-cv-21
Pickett, Theodore	Pickett, Theodore	12-cv-2121
Bowden, Gregory	Bowden, Gregory	12-cv-2127
Kniffen, Donna Lee	Kniffen, Donna	12-cv-2150
Hamman, Janet	Hamman, Janet	12-cv-2189
Steinert, Julie	Steinert, Julie	12-cv-22
Lynch, Kiersten	Lynch, Kiersten	12-cv-2210
Dunn, Lucille	Dunn, Lucille	12-cv-2211
Nelson, Susan	Nelson, Susan	12-cv-2258
Lindenmeier, Janet	Lindenmeier, Janet	12-cv-2265
DeStefano, Loretta	DeStefano, Loretta	12-cv-2266
Anderson, Joseph	Anderson, Barbara (PR-Joseph Anderson Estate)	12-cv-227

Plaintiff Name	Case Name	Case No.
Lopes, Mary Carolyn	Lopes, Mary	12-cv-23
Frye, Barbara	Frye, Barbara	12-cv-2302
Sutherland, Evelyn	Sutherland, Evelyn	12-cv-2328
Sandfort, Irma	Sandfort, Irma	12-cv-2371
Odum, Connie	Odum, Connie	12-cv-2451
Gilbert, Barbara	Gilbert, Barbara	12-cv-2547
Karimi-Azad, Talat	Karimi-Azad, Talat	12-cv-2548
Latta, Theresa	Latta, Theresa	12-cv-2549
Kirkpatrick, Judy	Kirkpatrick, Judy	12-cv-2559
Canaday, Connie	Canaday, Connie	12-cv-2560
Edwards, Donna	Edwards, Donna	12-cv-2561
Lackey, Karen	Lackey, Karen	12-cv-2594
Evans, Dorothy	Evans, Dorothy	12-cv-2596
Brown, Towanda	Brown, Towanda	12-cv-2598
Himalaya, Shanthi	Himalaya, Shanthi	12-cv-2599
Tressler, Vera	Tressler, Vera	12-cv-2600
Heldberg, Judith	Heldberg, Judith	12-cv-2647
Campbell Carter, Marguerite	Carter, Marguerite	12-CV-2674
Nesbitt, Craig	Nesbitt, Craig	12-cv-268

Plaintiff Name	Case Name	Case No.
Coventry, Melinda	Coventry, Melinda	12-cv-269
Adams, Brenda	Adams, Brenda	12-cv-270
Yancu, Milly	Yancu, Milly	12-cv-271
Franklin, Suzane	Franklin, Suzane	12-cv-272
Davis, Patricia	Davis, Patricia	12-cv-273
Brown, Garry L.	Brown, Garry	12-cv-2731
Hen, Azucena	Hen, Azucena	12-cv-2771
Foland, Judith	Foland, Bobbie (PR-Judith Foland Estate)	12-cv-278
Sias, Diana Van Pelt Newell	Sias, Diana Van Pelt Newell	12-cv-2833
Otto, Harriet	Otto, Harriet	12-cv-2837
Best, Bettie J.	Best, Bettie	12-cv-2838
Davis, Betty	Davis, Betty Saki	12-cv-3017
Roberts, Margaret	Roberts, Margaret	12-cv-3021
Goias, Geraldine	Goias, Geraldine	12-cv-3022
Lona, Lucille	Lona, Lucille	12-cv-3023
McMurray, Deborah	McMurray, Deborah	12-cv-3025
Doriott, Angelita	Doriott, Angelita	12-cv-3026
Thieman, Donna	Thieman, Donna	12-cv-3027
Stanley, Betty	Stanley, Betty	12-cv-3052

Plaintiff Name	Case Name	Case No.
Gerardo, Claudia	Gerardo, Claudia	12-cv-310
Mueller, Eileen	Mueller, Eileen	12-cv-312
White, Claudia	Welch, Patrick - 2012	12-cv-3259
Eshelman, Stephanie	Eshelman, Stephanie	12-cv-3260
Grillo, Maria	Grillo, Maria	12-cv-3261
Albrecht, Doris	Albrecht, Doris	12-cv-3287
Black, Sandra Y.	Black, Sandra	12-cv-33
Bjork, Frances	Bjork, Frances	12-cv-3325
Gerber, Marilyn	Gerber, Marilyn	12-cv-3326
Niver, Clara	Niver, Clara	12-cv-3327
Tong, Lucy	Tong, Lucy	12-cv-3328
Venner, Vida	Venner, Vida	12-cv-3329
Uslan, Sharon	Uslan, Sharon	12-cv-3330
Goldberg, Ethel	Goldberg, Ethel	12-cv-3331
Hudson, Laraine	Hudson, Laraine	12-cv-3335
Rittenhouse, Carolyn	Rittenhouse, Carolyn	12-cv-3345
Budd, Randal	Budd, Randal	12-cv-3346
Myers, Eva	Myers, Eva	12-cv-3347
Dykes, Marsha	Dykes, Marsha	12-cv-3348
Foree, Edith	Foree, Edith	12-cv-3358
Indich, Terry E.	Indich, Terry	12-cv-3366
Diaz, Ana	Diaz, Ana	12-cv-3386

Plaintiff Name	Case Name	Case No.
Travor, Lois Annette	Travor, Lois Annette	12-cv-3399
Steen, Barbara	Steen, Barbara	12-cv-3429
Charms, Shirley	Charms, Shirley	12-cv-3511
Burch, Margaret	Burch, Margaret	12-cv-3554
Denham, Janice	Denham, Janice	12-cv-3696
Tanglao, Lourdes	Tanglao, Lourdes	12-cv-3705
Disosway, Linda	Disosway, Linda	12-cv-3730
Weiss, Linda	Weiss, Linda	12-cv-374
Hunt, Betty Burch	Hunt, Betty Burch	12-cv-375
Murphy, Elaine L.	Murphy, Elaine	12-cv-376
Lare, Sandra	Lare, Sandra	12-cv-3769
Ferguson, Marion A.	Ferguson, Marion	12-cv-377
Nealen, Arlene	Nealen, Arlene	12-cv-3770
DerHarootunian, Carolyn	DerHarootunian, Carolyn	12-cv-3789
Vocci, Nancy	Vocci, Nancy	12-cv-3790
Yacoub, Caroline	Yacoub, Caroline	12-cv-3795
Baker, Alma	Baker, Alma	12-cv-3878
Palma, Lucita	Palma, Lucita	12-cv-3879
Mateo, Yoshie	Mateo, Yoshie	12-cv-3904
Eisen, Ella	Eisen, Ella	12-cv-391

Plaintiff Name	Case Name	Case No.
Rangel, Elvia	Rangel, Elvia	12-cv-392
Hill, Mary	Hill, Mary	12-cv-3959
Wilson, Selma N.	Wilson, Selma	12-cv-4014
Thomasson, Patsy Mae	Thomasson, Patsy Mae	12-cv-403
Schendle, Carolyn	Schendle, Carolyn	12-cv-404
Toland, Kathleen	Toland Kathleen	12-cv-4190
Russell, Diana	Russell, Diana	12-cv-4266
Filippello, Margaret	Filippello, Margaret	12-cv-4423
Harris, Ramona	Harris, Ramona	12-cv-4424
Caffery, Sharil	Caffery, Sharil	12-cv-4425
Lane, Sharon	Lane, Sharon	12-cv-4426
Whisenant, Louise	Whisenant, Louise	12-cv-4440
Glenn, Sue Ellen	Glenn, Sue	12-cv-4454
Sweet, Karen	Sweet, Karen	12-cv-4566
Hutton, Nancy	Hutton, Nancy	12-cv-4599
Hernandez, Antonia Maria	Hernandez, Antonia	12-cv-4601
Favor, Judith	Favor, Judith	12-cv-4604
Enfield, Sandra	Harralson, Connie (PR-Leta Sneed Estate)	12-cv-4608

Plaintiff Name	Case Name	Case No.
Whiteside, Elizabeth	Whiteside, Elizabeth	12-cv-4609
Parker, Esther	Parker, Esther	12-cv-4611
Mitchell, Cheryl	Mitchell, Cheryl	12-cv-4638
Hogan, Charlotte	Hogan, Charlotte	12-CV-464
Paralikis, Pamela	Paralikis, Pamela	12-cv-4656
Bottari, Donna	Bottari, Donna	12-cv-4663
Hedgepeth, Betty	Hedgepeth, Betty	12-cv-4664
Sperber, Bernice	Sperber, Bernice	12-cv-4721
Worthington, Jerrene	Worthington, Jerrene	12-cv-4762
Patrina, Margaret	Patrina, Chester (PR-Margaret Patrina Estate)	12-cv-4773
Falcone, Patrica	Falcone, Patricia	12-cv-4802
Anselmo, Victoria	Anselmo, Victoria	12-cv-4806
Patterson, Ethel	Patterson, Ethel	12-cv-4836
Carter, Katherine S.	Carter, Katherine	12-cv-4940
Feingold, Renee	Feingold, Renee	12-cv-4941
Haslam, Martha	Haslam, Martha	12-cv-5018
Julius, Diana	Julius, Diana	12-cv-5019
Mott, LeAnn	Mott, Leann	12-cv-5020

Plaintiff Name	Case Name	Case No.
Baldridge, Wilemina	Baldridge, Wilemina	12-cv-503
McCabe, Doreen	McCabe, Doreen	12-cv-504
McCabe, Judith Bachelor	McCabe, Judith	12-cv-508
Walker, Shirley	Walker, Shirley	12-cv-5085
Bedsworth, Reba	Bedsworth, Alan (PR-Reba Bedsworth Estate)	12-cv-5094
Owens, Janene Kay	Owens, Janene	12-cv-5101
McGowan, Christine	McGowan, Christine	12-cv-5105
Crew, Nellie	Crew, Nellie	12-cv-5108
Quinlan, Barbara J.	Quinlan, Barbara	12-cv-5332
Kovalick, Carole	Kovalick, Carole	12-cv-5354
Knutson, Josephine	Knutson, Josephine	12-cv-5383
Smith, Regina	Smith, Regina	12-cv-5384
Cronic, Lura Lee A.	Hamilton-Gamman, Sandra Lynn (PR-Lura Lee A. Cronic Estate)	12-cv-5385
Logsdon, Adele	Logsdon, Adele	12-cv-5386

Plaintiff Name	Case Name	Case No.
Needles, Josephine	Needles, Josephine	12-cv-5389
Kendrick, Billie J.	Kendrick, Billie	12-cv-5391
Paxton, Mary	Paxton, Mary	12-cv-5392
Stanwood, Peggy	Stanwood, Peggy	12-cv-5393
Ellis, Rosemary	Ellis, Rosemary	12-cv-5429
Shull, Mary Anne	Shull, Mary Anne	12-cv-5473
Knopick, Carol	Knopick, Carol	12-cv-5485
Logan, Joyce	Logan, Joyce	12-cv-5553
Shulkin, Audrey	Shulkin, Audrey	12-cv-5554
Pitts, Jamie	Pitts, Jamie	12-cv-5556
Osburn, Gaile	Osburn, Gaile	12-cv-5557
Guire, Hazel	Guire, Hazel	12-cv-5559
Miller, Dolores	Miller, Dolores	12-cv-5560
Williams, Carleen	Williams, Carleen	12-cv-5561
Hill, Phyllis	Harne, Sharon (PR-Phyllis Hill Estate)	12-cv-5562
Drake, Elaine	Drake, Elaine	12-cv-5563
Griffin, Sally	Griffin, Sally	12-cv-5579
Heckard, Shirley	Heckard, Shirley	12-cv-5581
Akridge, Ronald	Akridge, Ronald	12-cv-5591
Huenefeld, Catherine	Huenefeld, Catherine	12-cv-564

Plaintiff Name	Case Name	Case No.
Stiles, Brenda M.	Stiles, Brenda	12-cv-5640
Goldberger, Esther	Goldberger, Esther	12-cv-5643
Gregori, Carolyn	Gregori, Carolyn	12-cv-566
Rhodes, Ardeth	Rhodes, Ardeth	12-cv-5663
Heinonen, Marie	Heinonen, Marie	12-cv-567
Rath, Carolyn	Rath, Carolyn	12-cv-568
Cline, Diane	Cline, Diane	12-cv-5681
Rousey, Shirlie	Rousey, Shirlie	12-cv-569
Simpson, Esther	Simpson, Esther	12-cv-570
Wilson, Sharon	Wilson, Sharon	12-cv-571
Stotts, Wilma	Stotts, Wilma	12-cv-572
Cummings, Sarah	Cummings, Sarah	12-cv-5776
Caldarello, Madeline	Caldarello, Madeline	12-cv-5832
Villadiego, Maria	Villadiego, Maria	12-cv-5833
Ziegenfus, Gwendolyn	Ziegenfus, Gwendolyn	12-cv-5834
Allen, Juanita	Allen, Juanita	12-cv-5835
Fox, Dorothy	Fox, Dorothy	12-cv-5836
Everly, Myrna	Everly, Myrna	12-cv-588
Kraynick, Judith	Kraynick, Judith	12-cv-589
Begany, Helen	Begany, Helen	12-cv-590

Plaintiff Name	Case Name	Case No.
Finn, Barbara	Finn, Barbara	12-cv-591
Scott, Lois	Scott, Lois	12-cv-592
Migatulski, Mary	Migatulski, Mary	12-cv-593
Reitz, Alice	Reitz, Alice	12-cv-594
Cooper, Eva	Cooper, Eva	12-cv-595
Mora, Maria	Mora, Maria	12-cv-5965
Putman, Betty	Putman, Betty	12-cv-5969
Jodszuweit, Armida	Jodszuweit, Armida	12-cv-5975
Brail, Katherine	Brail, Katherine	12-cv-5977
Collier, Nancy	Collier, Nancy	12-cv-5978
Sayers, Sheila	Sayers, Sheila	12-cv-5993
Wiegand, Mary	Wiegand, Mary	12-cv-6029
Holman, Richlyn L.	Holman, Richlyn	12-cv-6051
McMillan, Earline	McMillan, Earline	12-cv-6065
Stone, Gladys O.	Stone, Gladys	12-cv-6066
Eversole, Connie	Eversole, Connie	12-cv-6100
Burnett, Mary	Burnett, Mary	12-cv-6101
Hofer, Dolores	Hofer, Dolores	12-cv-6103
Roland, Annie	Roland, Annie	12-cv-6155
Rivers, Patricia	Rivers, Roland (PR-Patricia Rivers Estate)	12-cv-6156

Plaintiff Name	Case Name	Case No.
Olson, Corinne	Olson, Corinne	12-cv-6157
O'Donnell, Michele	O'Donnell, Michele	12-cv-6158
Moosally, Beatrice	Moosally, Beatrice	12-cv-6159
Melven, Carmela	Melvin, Carmela	12-cv-6160
Kozla, Marianne	Kozla, Marianne	12-cv-6162
Gunsberg, Melvin	Gunsberg, Melvin	12-cv-6163
Castillo, Frances	Castillo, Frances	12-cv-6165
Breslin, Frances	Breslin, Frances	12-cv-6166
Kazemi, Marilyn	Kazemi, Marilyn	12-cv-6183
Koski, Solita	Koski, Solita	12-cv-6184
Morgan, Lila	Morgan, Lila	12-cv-6185
Perkins, Yolanda	Perkins, Yolanda	12-cv-6186
Wong, Anita	Wong, Anita	12-cv-6187
Pidluski, Olga	Pidluski, Olga	12-cv-6188
Martin, Bobbie	Martin, Bobbie	12-cv-6189
Lowe, Georgetta	Lowe, Georgetta	12-cv-6190
Hayden, Jane	Hayden, Jane	12-cv-6191
McGrath, Sheila	McGrath, Sheila	12-cv-6192
Van Blaricom, Betty	Van Blaricom, Betty	12-cv-6216
Delagarza, Margaret	Delagarza, Margaret	12-cv-622

Plaintiff Name	Case Name	Case No.
Shapiro, Ellen	Shapiro, Ellen	12-cv-623
Frangos, Artemis	Frangos, Artemis	12-cv-625
Freelin, Stephanie	Freelin, Stephanie	12-cv-626
Fuerstnau, Barbara	Fuerstnau, Barbara	12-cv-6264
Halfmann, Mary	Halfmann, Mary	12-cv-6266
Kimizuka, Yoshie	Kimizuka, Yoshie	12-cv-6267
Hofmann, Kathleen	Hofmann, Kathleen	12-cv-6269
Grassel, Sara	Grassel, Sara	12-cv-627
Sigro, Betty J.	Sigro, Betty	12-cv-6272
Frizzell, Martha	Frizzell, Martha	12-cv-6273
Duggan, Doris	Duggan, Doris	12-cv-6275
Halpern, Beverly	Halpern, Beverly	12-cv-628
Gunkle, Charlotte	Gunkle, Charlotte	12-cv-6285
Andorka-Aceves, Deborah	Andorka-Aceves, Deborah	12-cv-6289
Harvey, Robert	Harvey, Robert	12-cv-629
Modrow, Shirley	Modrow, Shirley	12-cv-6293
Stewart, Kathleen	Stewart, Kathleen	12-cv-6296
Hunter, Daphne	Hunter, Daphne	12-cv-6300

Plaintiff Name	Case Name	Case No.
O'Neal, Linda	O'Neal, Linda	12-cv-6302
Jones, Renae	Jones, Renae	12-cv-631
Barbe, Jane	Barbe, Jane	12-cv-6348
Denmon, Sterling	Denmon, Sterling	12-cv-6350
Delikat, Ellen	Delikat, Ellen	12-cv-6351
Taylor, Linda	Taylor, Linda	12-cv-6364
Mouser, Donna	Mouser, Donna	12-cv-6365
Hulsman, Elaine	Hulsman, Elaine	12-cv-6366
Cox, Mary Ann	Cox, Mary Ann	12-cv-6367
Kempfer, Faye	Kempfer, Faye	12-cv-6376
Irving, Zepher	Irving, Zepher	12-cv-6397
Rich-D'Andrea, Jeanine	Irving, Zepher	12-cv-6397
Steiner, Harriet	Irving, Zepher	12-cv-6397
Singh, Priscilla	Singh, Priscilla	12-cv-640
Mays, Imogene	Mays, Imogene	12-cv-6408
Mercer, Ruby	Mercer, Ruby	12-cv-6425
Worthington, Renee	Worthington, Renee	12-cv-643
Marcus, Rita	Marcus, Rita	12-cv-6430
Halpern, Marion	Halpern, Marion	12-cv-6432
Bittner, Marcella	Bittner, Marcella	12-cv-6434
Wade, Kay	Wade, Kay	12-cv-6437
Palmer, Richard	Palmer, Richard	12-cv-644

Plaintiff Name	Case Name	Case No.
Boshell, Marsha	Boshell, Marsha	12-cv-6441
Holmes, Leanne	Holmes, Leanne	12-cv-6445
Napoli, Anna	Napoli, Anna	12-cv-6446
James, Claudia	James, Claudia	12-cv-645
Vaughn, Patricia	Vaughn, Patricia	12-cv-6450
Irizarry, Sheila	Irizarry, Sheila	12-cv-6451
Kosvick, Melinda	Kosvick, Melinda	12-cv-6454
Homa, Barbara	Homa, Barbara	12-cv-6455
Stepanski, Mary Jo	Stepanski, Mary Jo	12-cv-6456
Nguyen, Susan	Nguyen, Susan	12-cv-6458
Jeet, Lalita	Jeet, Lalita	12-cv-6459
Naik, Khadijah	Naik, Khadijah	12-cv-6460
Bartlett, Ann	Bartlett, Ann	12-cv-6461
Aydin, Jean	Aydin, Jean	12-cv-6462
Van Gosen, Helen	Van Gosen, Helen	12-cv-6464
Huddleston, Shirley	Huddleston, Shirley	12-cv-6465
Griffin, Jennifer	Griffin, Jennifer	12-cv-6466
Crisci, Sarah	Crisci, Stephen (PR-Sarah Crisci Estate)	12-cv-6469
Kozloski, Margaret	Kozloski, Margaret	12-cv-647
Fishel, Patricia	Fishel, Patricia	12-cv-6470

Plaintiff Name	Case Name	Case No.
Matthews, Roxie Mogler	Matthews, Roxie Mogler	12-cv-648
Newman, Lula	Newman, Lula	12-cv-649
Dirks, Susan	Dirks, Susan	12-cv-650
Carpenter, Julia Ann	Carpenter, Julia Ann	12-cv-651
Perlow, Liba	Perlow, Liba	12-cv-6520
Madary, Roberta	Madary, Roberta	12-cv-654
Rimstidt, Nelda	Rimstidt, Nelda	12-cv-655
Jones, Geraldine	Jones, Geraldine	12-cv-6550
Taylor, Sherri	Taylor, Sherri	12-cv-656
Sprangler, Katherine	Sprangler, Katherine	12-cv-6562
Balsam, Barbara	Balsam, Barbara	12-cv-657
Mester, Dorothy	Mester, Dorothy	12-cv-658
Raven, Arleen	Raven, Arleen	12-cv-659
Garrett, Barbara	Garrett, Barbara	12-cv-660
Johnson, Karen	Johnson, Karen	12-cv-6600
Dwyer, Marion	Dwyer, Marion	12-cv-663
Eck, Marlene	Eck, Marlene	12-cv-664
Uselton, Lynnita	Uselton, Lynnita	12-cv-665
Piwinski, Dianne	Piwinski, Dianne	12-cv-6654
Ayres, Catherine	Ayres, Catherine	12-cv-6658
Still, Nanette	Still, Nanette	12-cv-666
Gittelman, Iris	Gittelman, Iris	12-cv-6660

Plaintiff Name	Case Name	Case No.
Wheeler, Jo	Wheeler, Jo	12-cv-667
McKinney, Carlene	McKinney, Carlene	12-cv-6711
Karantza, John	Karantza, John	12-cv-6719
Darling, Selma	Darling, Selma	12-cv-6799
Cline, Beatrice	Wells, Melody Ann (PR-Beatrice Cline Estate)	12-cv-6840
Broadstone, Judith	Broadstone, Judith	12-cv-6841
Atkins, Peggy	Atkins, Peggy	12-cv-6842
Schmitt, Luise Gerlinde	Schmitt, Luise Gerlinde	12-cv-6845
Cherco, Patricia	Cherco, Patricia	12-cv-6846
Neuman, Janet	Neuman, Janet	12-cv-6850
Ennever, Patricia	Foster, Hazel	12-cv-6857
Foster, Hazel	Foster, Hazel	12-cv-6857
Ledbetter, David	Foster, Hazel	12-cv-6857
Porter, Angela	Foster, Hazel	12-cv-6857
Isom, Leann	Isom, Leann	12-cv-6859
Heiny, Joyce	Heiny, Joyce	12-cv-6860
Vertuccio, Lana	Vertuccio, Lana	12-cv-6863
Upton, Margaret	Upton, Margaret	12-cv-6878
Welty, Johanna Peters	Welty, Johanna	12-cv-6879

Plaintiff Name	Case Name	Case No.
Smith, Richard	Smith, Richard	12-cv-688
Bucher, Rose	Bucher, Rose	12-cv-689
Oveson, Carolyn	Oveson, Carolyn	12-cv-6898
Stevenson, Nada	Stevenson, Nada	12-cv-6899
Elison, Linda	Elison, Linda	12-cv-6900
Lingo, Melba	Lingo, Melba	12-cv-6901
Baylor, Richard	Baylor, Richard	12-cv-6903
Thompson, Loralee	Thompson, Loralee	12-cv-6905
Miller, Esther	Miller, Esther	12-cv-6907
Jeffery, Joy	Jeffery, Joy	12-cv-6908
Goheen, Patty	Goheen, Patty	12-cv-691
Powers, Peggy	Powers, Peggy	12-cv-692
Muller, Eleanor	Muller, Eleanor	12-cv-693
Lemley, Sheila	Lemley, Sheila	12-cv-694
Townsend, Thomas	Townsend, Thomas	12-cv-6942
Monahan, Virginia	Monahan, Virginia	12-cv-6943
Basile, Marie	Basile, Marie	12-cv-6944
Maurice, Elisabeth Vail	Maurice, Elisabeth Vail	12-cv-6947
Curry, Nellie	Curry, Nellie	12-cv-695
Orr, June	Orr, June	12-cv-6952
Patterson, Carole	Patterson, Carole	12-cv-6953

Plaintiff Name	Case Name	Case No.
Maki, Gale	Maki, Gale	12-cv-6954
Collins, John	Collins, John	12-cv-6955
McAnulty, Joan	McAnulty, Joan	12-cv-6956
Abney, Virginia	Abney, Virginia	12-cv-6957
Phillips, Majorie	Phillips, Majorie	12-cv-6958
Hurley, Cheryl	Hurley, Cheryl	12-cv-6985
Altson, Amy R.	Altson, Amy	12-cv-7023
Harris, Kenneth	Harris, Hope (PR-Kenneth Harris Estate)	12-cv-7048
Thomas-Walsh, Theresa	Thomas-Walsh, Theresa	12-cv-707
Pickering, Linda	Pickering, Linda	12-cv-7111
Cook, Darlene	Cook, Darlene	12-cv-7112
Epstein, Marilyn	Epstein, Marilyn	12-cv-7113
Millar, Orah	Millar, Orah	12-cv-7124
Gonshor, Eleanor	Gonshor, Eleanor	12-cv-7125
Swanson, Nancy	Swanson, Nancy	12-cv-714
Cox, Ralph T.	Cox, Ralph T.	12-cv-7173
Kershanbaum, Roslyn	Kershanbaum, Roslyn	12-cv-7192
Dale, Marcia "Marcy"	Dale, Marcia	12-cv-7193
Deaver, Clarice A.	Deaver, Clarice	12-cv-7252
Jones, Sumi	Jones, Sumi	12-cv-7256

Plaintiff Name	Case Name	Case No.
Morissette, Carol	Morissette, Carol	12-cv-7258
Ecker, Susan	Ecker, Susan	12-cv-7259
Roberts, Sandra	Roberts, Sandra	12-cv-7286
Carter, Cristina	Carter, Cristina	12-cv-7331
Faust, Patricia	Faust, Patricia	12-cv-7365
Ryder, Eleanor	Ryder, Eleanor	12-cv-7375
Egle, Mary Frances	Egle, Mary	12-cv-7376
Eppler, Patricia	Eppler, Patricia	12-cv-7411
Gillett, Margaret	Gillett, Margaret	12-cv-7412
Gurth, Beverly	Gurth, Beverly	12-cv-7413
Pace, Phyllis	Pace, Phyllis	12-cv-7414
Burchett, Priscilla	Burchett, Priscilla	12-cv-7416
Croyle, Kim	Croyle, Kim	12-cv-7417
Karones, Clara	Karones, Clara	12-cv-7418
Luck, Mary	Luck, Mary	12-cv-7419
Hampson, Rosemary	Hampson, Rosemary	12-cv-7420
Rensing, Christine	Lowry, Marion (PR-Christine Rensing Estate)	12-cv-7421
Jones, Sheila	Jones, Sheila	12-cv-7422
Narr, Colleen	Narr, Colleen	12-cv-7425
Torp, Mary Ann	Torp, Mary Ann	12-cv-7426

Plaintiff Name	Case Name	Case No.
Jones, Carole	Jones, Carole	12-cv-7427
Jaeger, Bernadette	Jaeger, Bernadette	12-cv-7443
Pearson, Linda	Pearson, Linda	12-cv-750
LeMasters, Terri M.	LeMasters, Terri	12-cv-7542
Maurstad, Karen	Maurstad, Karen	12-cv-7645
Psyck, Carolyn	Psyck, Carolyn	12-cv-7684
Ray, Susan	Ray, Susan	12-cv-7721
Colern, Barbara	Colern, Barbara	12-cv-7723
Couture, Diane	Couture, Diane	12-cv-7819
Shepherd, Madge	Shepherd, Madge	12-cv-82
Savoy, Josephine	Savoy, Josephine	12-cv-855
Montgomery, Rulene	Montgomery, Rulene	12-cv-877
Gentile, Emma	Gentile, Emma	12-cv-928
Walker, Sherry Meeks	Walker, Sherry	12-cv-943
Estes, Bobbie Jean Wood	Richmond, Nancy M.	12-cv-946
Richmond, Nancy M.	Richmond, Nancy M.	12-cv-946
Giarratano, Ruth	Giarratano, Ruth	12-cv-960

Plaintiff Name	Case Name	Case No.
Wicher, Helen	Wicher, Deborahanne (PR for Estate of Wicher, Helen)	12-cv-964
Lange, Vera	Lange, Susan (PR-Vera Lange Estate)	12-cv-966
Meldon, Virginia "Jackie"	Meldon, Virginia	12-cv-974
Davis, Melissa (Mary Melissa)	Davis, Melissa	13-1-cv-5324
VanDyke, Patricia	VanDyke, Patricia	13-cv-1
Bray, Nettie	Bray, Nettie	13-cv-1017
Bartsch, Geraldine	Bartsch, Geraldine	13-cv-1021
Albert, Elizabeth	Albert, Elizabeth	13-cv-1062
Hawk, Joycelyn	Hawk, Joycelyn	13-cv-1063
Pritchard, Helen	Pritchard, Helen	13-cv-1071
Schwartz, Marilyn	Schwartz, Marilyn (femur fracture)	13-cv-1155
Rampell, Arlene A.	Rampell, Arlene	13-cv-1194
O'Brien, Delores Marie	O'Brien, Delores Marie	13-cv-1197
Abrams, Marilyn	Abrams, Marilyn	13-cv-120
Lipscomb, Joan	Lipscomb, Joan	13-cv-121

Plaintiff Name	Case Name	Case No.
Myers, Susan S.	Myers, Susan	13-cv-1215
Levi, Eva	Levi, Eva	13-cv-122
Falconieri, Diane	Falconieri, Diane	13-cv-1240
Landis, Jacqueline	Landis, Jacqueline	13-cv-1241
Meltzer, Yvette	Meltzer, Yvette	13-cv-1243
Powers, Kaaren	Powers, Kaaren	13-cv-1245
Sherwood, Myrna	Sherwood, Myrna	13-cv-1246
Stanton, Rosemary	Stanton, Rosemary	13-cv-1247
Stecher, Donald	Stecher, Donald	13-cv-1248
Carbo, Dorothy	Carbo, Dorothy	13-cv-1260
Abee, Helen	Abee, Helen	13-cv-1263
White, Sammy	White, Sammy	13-cv-1296
Betts, Sandra	Betts, Sandra	13-cv-1297
Mosner, Florence	Mosner, Florence	13-cv-1299
Brooks, Betty	Brooks, Betty	13-cv-1314
Breen, Mary Elizabeth	Breen, Mary Elizabeth	13-cv-1316
Bowen, Kay	Bowen, Kay	13-cv-1317
Retsel, Mary Jean	Retsel, Mary Jean	13-cv-1322
Powers, Emily Earle	Powers, Emily	13-cv-1323

Plaintiff Name	Case Name	Case No.
Southard, Charles	Southard, Charles	13-cv-1325
Hawkins, Amy	Hawkins, Amy	13-cv-1337
Smith, Marguerite	Mills, Cheryl (PR-Marguerite Smith Estate)	13-cv-1339
Edmondson, Maxine	Edmondson, Maxine	13-cv-1340
Kamienski, Mary	Kamienski, Mary	13-cv-1352
Hancock, Judith	Gordan, Michelle (PR-Judith Hancock Estate)	13-cv-1361
Parr, Loyce Marlene	Parr, Loyce Marlene	13-cv-1362
Gunderson, Rose	Gunderson, Rose	13-cv-1366
James, Betty	James, Betty	13-cv-1367
Neuman, Delores	Neuman, Delores	13-cv-1369
Antoff, Christine	Antoff, Christine	13-cv-137
Peters, Alohoa	Peters, Alohoa	13-cv-1370
Routhieaux, Marguerite	Routhieaux, Marguerite	13-cv-1371
Alberg, Evelyn	Alberg, Evelyn	13-cv-1378
Krupka, Marianne B.	Krupka, Marianne	13-cv-1411

Plaintiff Name	Case Name	Case No.
Bartosch, Nancy J.	Bartosch, Nancy	13-cv-1413
Goodman, Carol Ann	Goodman, Carol Ann	13-cv-1415
Kantrowitz, Norma	Kantrowitz, Norma	13-cv-1420
Mymit, Florence	Mymit, Florence	13-cv-1421
Southard, Marjorie	Southard, Charles (PR-Marjorie Southard Estate)	13-cv-1428
Colby, Carol A.	Colby, Carol	13-cv-1435
Bush, Juanita	Bush, Juanita	13-cv-1448
Osburn, Kathryn	Osburn, Kathryn	13-cv-1470
Samuelson, Johann E.	Samuelson, Johann	13-cv-1476
Riley, Carol A.	Riley, Carol	13-cv-1477
Anaya, Prescilla	Griggs-Anaya, Eleanor (PR-Prescilla Anaya Estate)	13-cv-1487
Nance, Mardi	Nance, Mardi	13-cv-1489
Frasier-Smith, Sandra K.	Frasier-Smith, Sandra	13-cv-1492
Sherry, Mary Ann	Sherry, Mary Ann	13-cv-1499

Plaintiff Name	Case Name	Case No.
Shaffer, Marilyn D.	Shaffer, Marilyn	13-cv-1511
Kellison, Joyce H.	Kellison, Joyce	13-cv-1513
Liddle, David A.	Liddle, David	13-cv-1514
Rempson, Andre D.	Rempson, Andre	13-cv-1515
Stark, Tavie G.	Stark, Tavie	13-cv-1517
Quinn, Nancy Mae	Quinn, Nancy Mae	13-cv-1518
Min, Pyohngsook	Min, Pyohngsook	13-cv-1521
Criss, Mira L.	Criss, Mira	13-cv-1524
Rees, Martha	Rees, Martha	13-cv-1526
Raczka, Nancy	Raczka, Nancy	13-cv-1588
Jennings, Madeline	Jennings, Madeline	13-cv-1592
Wanish, Dorothy	Wanish, Dorothy	13-cv-1593
Auker, Carolyn	Auker, Carolyn	13-cv-1657
Phillips, Linda	Phillips, Linda	13-cv-1658
Pardue, Ellis	Pardue, Ellis	13-cv-1659
Allera, June	Allera, June	13-cv-1661
Valdez, Beatrice	Valdez, Beatrice	13-cv-1662
Easterling, Dolores	Easterling, Dolores	13-cv-1687
Coffey, Jean E.	Coffey, Jean	13-cv-1696
Cruce, Eva	Cruce, Eva	13-cv-1698

Plaintiff Name	Case Name	Case No.
McGuire, Doris	McGuire, Doris	13-cv-170
Wyly, Lois Ann	Wyly, Lois Ann	13-cv-171
Cuedek, Steven	Cuedek, Steven	13-cv-1715
McNinch, Patricia E.	McNinch, Robert (PR-Patricia McNinch Estate)	13-cv-1717
Stubler, Madeline C.	Stubler, Madeline	13-cv-1718
Prout, Dorothy	Prout, Dorothy	13-cv-1728
Meiner, Gerald	Meiner, Gerald	13-cv-177
Conway, Janet	Conway, Janet	13-cv-179
McGarvey, Sheila	McGarvey, Sheila	13-cv-1866
Lapham, Joan	Lapham, Joan	13-cv-1869
Wilson, Emily	Wilson, Emily	13-cv-1872
Woodson, January Fern	Woodson, January Fern	13-cv-1883
Rudolph, Joyce	Rudolph, Joyce	13-cv-1884
Haynes, TC	Haynes, TC	13-cv-1885
McCoy, Elizabeth	McCoy, Elizabeth	13-cv-1886
Goldman, Marlene	Goldman, Marlene	13-cv-1890
Duncan, Mary	Duncan, Mary	13-cv-1891
Krapek, Lynn Ann	Krapek, Lynn Ann	13-cv-20
Collins, Margie	Collins, Margie	13-cv-2004

Plaintiff Name	Case Name	Case No.
Elmore, Dolly G.	Elmore, Dolly	13-cv-2089
Nelson, Marie S.	Nelson, Marie	13-cv-2092
Cromwell, Theresa	Cromwell, Theresa	13-cv-2095
Goodwin, Prudence	Goodwin, Prudence	13-cv-2096
Smith, Elizabeth	Smith, Elizabeth	13-cv-2097
Williams, Marjorie	Williams, Marjorie	13-cv-2098
Fleetwood, Stella	Fleetwood, Stella	13-cv-2108
Snow, Mary	Snow, Mary	13-cv-2109
Costigan, Jack	Costigan, Jack	13-cv-2159
Montana, Michael	Montana, Michael	13-cv-2209
Simic, Ann	Simic, Ann	13-cv-2211
Horn, Kathleen	Horn, Kathleen	13-cv-2224
Christy, Tamsen	Christy, Tamsen	13-cv-2246
LaFave, Darlene	La Fave, Darlene	13-cv-2287
Cassatt, Darlene	Cassatt, Darlene	13-cv-2401
Carey, Patricia	Carey, Patricia	13-cv-2413
Prinzel, Shirley	Prinzel, Shirley	13-cv-2471
Thompson, Claire	Thompson, Claire	13-cv-2564
Romeo, Alice	Romeo, Alice	13-cv-2616
Grems, Mary	Grems, Mary	13-cv-2617

Plaintiff Name	Case Name	Case No.
Yu, Nancy	Yu, Nancy	13-cv-2623
Camp, Phyllis	Camp, Phyllis	13-cv-2624
Hastings, Susan	Hastings, Susan	13-cv-2625
McKeon-Cincotta, Lena	McKeon-Cincotta, Lena	13-cv-2649
Lindsey, Yasuko	Lindsey, Yasuko	13-cv-2703
Kitowski, Charlene	Kitowski, Charlene	13-cv-2704
Presnall, Annie Sue	Presnall, Annie Sue	13-cv-2705
Jernigan, Mary Lou	Jernigan, Mary Lou	13-cv-2735
Mieczkowski, Alice	Mieczkowski, Alice	13-cv-2751
Geyer, Suzanne	Geyer, Suzanne	13-cv-2774
Gleue, Elmer	Gleue, Elmer	13-cv-2798
Wicker, Marie	Wicker, Marie	13-cv-2827
Stampliakas, Helen	Stampliakas, Helen	13-cv-2836
Thompson, Deborah	Stampliakas, Helen	13-cv-2836
Culpepper-Sheffield, Effie	Culpepper-Sheffield, Effie	13-cv-29
Crook, Judith L.	Crook, Judith	13-cv-2958
Dillard, Norma	Dillard, Norma	13-cv-30
Feinberg, Stephanie	Feinberg, Stephanie	13-cv-31

Plaintiff Name	Case Name	Case No.
Rydell, Sandra	Rydell, Sandra	13-cv-32
London, Phyllis	London, Phyllis	13-cv-3211
Rogers, Eugenia	Rogers, Eugenia	13-cv-3274
Vithespongse, Saichol	Vithsepongse, Saichol	13-cv-33
Connor, Ruth L.	Connor, Ruth	13-cv-3342
Mulqueen, Mary P.	Mulqueen, Mary	13-cv-3353
Hasty, Madeline Anne	Hasty, Madeline Anne	13-cv-3361
Weinmann, Shirley	Weinmann, Shirley	13-cv-34
Hazelbaker, Dorothy	Hazelbaker, Dorothy	13-cv-3443
Young, Terry	Young, Terry	13-cv-3464
Bravo de Meneses, Maria M.	Bravo de Meneses, Maria	13-cv-3471
Bergmann, Ruth	Bergmann, Ruth	13-cv-3474
Hudak, Mary	Hudak, Mary	13-cv-3475
Galemba, Ruth	Galemba, Ruth	13-cv-35
Hawes, Katherine	Hawes, Katherine	13-cv-36
Jatcko, Barbara	Jatcko, Barbara	13-cv-37
Spallone, Josephine	Spallone, Josephine	13-cv-3741

Plaintiff Name	Case Name	Case No.
Vanark, Elizabeth	Vanark, Elizabeth	13-cv-3887
Knecht, Rose	Knecht, Rose	13-cv-39
Maddern, Karen G.	Maddern, Karen	13-cv-3929
Lee, Chontella	Lee, Chontella	13-cv-40
McIntyre, Claude	McIntyre, Claude	13-cv-4043
Marcelles, Sara	Marcelles, Sara	13-cv-4075
Conroy, Joyce	Conroy, Joyce	13-cv-41
Rutman, Jane E.	Rutman, Jane	13-cv-4210
Matthews, Mary	Matthews, Mary	13-cv-4211
Conner, Cheryl	Conner, Cheryl	13-cv-442
Tidwell, Bryce Langston	Tidwell, Bryce Langston	13-cv-4447
Bennett, Elba I.	Bennett, Elba	13-cv-4448
Shevel, Faye Elizabeth	Shevel, Faye Elizabeth	13-cv-4577
Hawn, Patricia	Hawn, Patricia	13-cv-4643
Abbott, Sharon	Abbott, Sharon	13-cv-4701
Helfers, Myrtle A.	Helfers, Myrtle	13-cv-4985
Walker, Joanne	Walker, Joanne	13-cv-4986
Sohn, Sam	Sohn, Sam	13-cv-50
Defibaugh, Delores	Defibaugh, Delores	13-cv-5257
Dudek, Marjorie	Dudek, Marjorie	13-cv-5258

Plaintiff Name	Case Name	Case No.
Durec, Georgia	Durec, Georgia	13-cv-5259
Enerson, Kathleen	Enerson, Kathleen	13-cv-5260
Sellin, Joan	Sellin, Joan	13-cv-5261
Vanghel, Debra A.	Vanghel, Debra	13-cv-5264
Latini, Barbara	Latini, Barbara	13-cv-5299
Kafka, Helene	Kafka, Helene	13-cv-568
Salmons, Carmen	Salmons, Carmen	13-cv-5692
Capasso, Kathleen	Capasso, Kathleen	13-cv-5693
Gulley, Linda	Gulley, Linda	13-cv-5839
Chapman, Priscilla J.	Chapman, Priscilla	13-cv-590
Bernstein, Linda	Bernstein, Linda	13-cv-5911
Swasey, Martha Y.	Swasey, Martha	13-cv-593
Gann, Mary	Gann, Mary	13-cv-5943
Morey, Stella	Williamson-Robinette, Tammy (PR-Stella Morey Estate)	13-cv-5979
Tolston, Betty S.	Tolston, Betty	13-cv-5984
Voss, Margieann	Voss, Margieann	13-cv-6010
Stolt, Vera Mae	Stolt, Vera Mae	13-cv-6045

Plaintiff Name	Case Name	Case No.
Oakes, Miriam	Oakes, Miriam	13-cv-6090
Burns, Ruth M.	Burns, Ruth	13-cv-6183
Snyder, Janice L.	Snyder, Janice	13-cv-6184
Johnson, Beverly E.	Johnson, Beverly	13-cv-6205
Boue, Norma	Boue, Norma	13-cv-6406
Krebs, 12/3/2017	Krebs, Regina	13-cv-6407
Ahlgren, Constance	Ahlgren, Constance	13-cv-6546
Wallheimer, Sharon	Wallheimer, Sharon	13-cv-6563
Ostrowsky, Helena	Ostrowsky, Lynne (PR-Helena Ostrowsky Estate)	13-cv-694
Samuelson, Yvonne	Samuelson, Yvonne	13-cv-695
Henrich, Cetha	Henrich, Cetha	13-cv-698
Pannone, Anthony	Pannone, Anthony	13-cv-699
Zellers, Virginia L.	Zellers, Virginia	13-cv-7042
Moszczynski, Vera	Moszczynski, Vera	13-cv-7093
Harris, Nora Faye	Harris, Nora Faye	13-cv-7174

Plaintiff Name	Case Name	Case No.
Kardon, Koula	Kardon, Koula	13-cv-718
Mazariegos, Maria Enedelia	Mazariegos, Maria	13-cv-7186
Bialkowski, Mary V.	Bialkowski, Mary	13-cv-720
Reed, Patricia	Reed, Patricia	13-cv-736
George, Jean G.	George, Jean	13-cv-7414
Noel, Jill	Noel, Jill	13-cv-745
Salazar, Leonor	Salazar, Leonor	13-cv-747
Liston, Mary	Liston, Mary	13-cv-749
Chatman, Virginia	Chatman, Virginia	13-cv-754
Crunk, Dorothy	Crunk, Dorothy	13-cv-7563
Maher, Frances	Maher, Frances	13-cv-7622
Heaton, Sue	Heaton, Sue	13-cv-7705
Duval, Doris Jane	Duval, Doris	13-cv-772
Soria, Barbara	Soria, Barbara	13-cv-7824
Banner, Lorraine	Banner, Lorraine	13-cv-785
Wile, Lucille	Wile, Lucille	13-cv-7880
Burghardt, Pamela	Burghardt, Pamela	13-cv-7894
Schwartz, Mary M.	Schwartz, Mary	13-cv-812
Affronti, Joanne A.	Affronti, Joanne	13-cv-816

Plaintiff Name	Case Name	Case No.
Bannon, Gladys M.	Bannon, Gladys	13-cv-818
Enfield, Dorothy	Enfield, Dorothy	13-cv-830
Beadles, Louise	Beadles, Louise	13-cv-846
Lambert, Mary	Lambert, Mary	13-cv-851
Golden, Jane	Golden, Jane	13-cv-894
Wilke, Beverly	Wilke, Beverly	13-cv-925
Pitts, Shirley Ann	Pitts, Shirley Ann	13-cv-926
Slinkman, William Richard	Slinkman, William Richard	13-cv-928
Kessler, Janice Joanne	Kessler, Janice	13-cv-985
Wolschlager, Josephine	Wolschlager, Josephine	14-CV-03338
Ningas, Zenaida	Ningas, Zenaida	14-CV-0337
King, Lucy	King, Lucy	14-cv-04267
Fast, Joyce	Fast, Joyce	14-cv-04708
Brikha, Siranosh	Brikha, Siranosh	14-cv-04783
Smith, Nellie	Smith, Nellie	14-CV-06343
White, Wendy S.	White, Wendy	14-cv-1041
Brown, Christine	Brown, Christine	14-cv-1220
Hernandez, Enid	Hernandez, Enid	14-cv-1221
Mish, Dianna	Mish, Dianna	14-cv-1222

Plaintiff Name	Case Name	Case No.
Zick, Zelma	Zick, Terry (PR-Zelma Zick estate)	14-cv-1335
Beachel, Nancy	Beachel, Nancy	14-cv-1371
Turbes, Gerald	Turbes, Gerald	14-cv-1814
Paulson, Jo Ann	Paulson, Jo Ann	14-cv-1815
Quirk, William	Quirk, William	14-cv-1823
Webster, Dorothy Jane	Webster, Dorothy	14-cv-1916
Benoit, Carolyn F.	Benoit, Carolyn F.	14-cv-1917
Holland, Connie	Holland, Connie	14-cv-2147
Rasmusen, Martha	Rasmusen, Martha	14-cv-2148
Marasco, Joan P.	Marasco, Joan P.	14-cv-2624
White, Claudia	White, Claudia	14-cv-2717
Leeson-Pike, Elizabeth	Leeson-Pike, Elizabeth	14-cv-3365
Jackson, Helen	Johnson, Sandra (Estate of Helen Jackson)	14-cv-3763
Covin, Cynthia	Covin, Cynthia	14-cv-4308
Martin, Nancy	Martin, Nancy	14-cv-4326
Ausburn, Dorothy	Ausburn, Dorothy	14-cv-442
Marra, Carol A.	Marra, Carol A.	14-cv-4555
Eisman, Phyllis	Eisman, Phyllis	14-cv-4556

Plaintiff Name	Case Name	Case No.
Webb, Alberta A.	Webb, Alberta	14-cv-4557
Cichocki, Irene B.	Cichocki, Irene	14-cv-4558
Turski, Thressa	Turski, Thressa	14-cv-4559
Lundy, Heather A.	Lundy, Heather	14-cv-5575
Truong, Phan	Truong, Phan	14-cv-5750
Herrington, Juanita Knight Allen	Herrington, Juanita Knight Allen	14-cv-6064
Simpson, Judith	Simpson, Judith	14-cv-6081
Duvall, Joann	Duvall, Joann	14-cv-6088
Hunt, Arlene	Hunt, Arlene	14-cv-6717
Doses, Elaine	Doses, Elaine	14-cv-731
Person, Margaret	Person, Margaret	14-cv-7412
Blackwelder, Jo	Christian, Marilyn	14-cv-7542
Burns, Shelley	Christian, Marilyn	14-cv-7542
Christian, Marilyn	Christian, Marilyn	14-cv-7542
Clark, Janice	Christian, Marilyn	14-cv-7542
Darnell, Mary	Christian, Marilyn	14-cv-7542
Floyd, Shirley	Christian, Marilyn	14-cv-7542

Plaintiff Name	Case Name	Case No.
Gay, Kathleen	Christian, Marilyn	14-cv-7542
Hidalgo, Luisa	Christian, Marilyn	14-cv-7542
Hopper, Deborah	Christian, Marilyn	14-cv-7542
Jones, Mary	Christian, Marilyn	14-cv-7542
Lefevers, Betty	Christian, Marilyn	14-cv-7542
Maliwat, Elizabeth	Christian, Marilyn	14-cv-7542
McCaskill, Tanya	Christian, Marilyn	14-cv-7542
Metoxen, Deborah	Christian, Marilyn	14-cv-7542
Midgley, Carolyn	Christian, Marilyn	14-cv-7542
Mohler, Carole	Christian, Marilyn	14-cv-7542
Moore, Cheryl	Christian, Marilyn	14-cv-7542
Navin, Mary	Christian, Marilyn	14-cv-7542
Nelson, Mary Jane	Christian, Marilyn	14-cv-7542
Pate, Sarah	Christian, Marilyn	14-cv-7542

Plaintiff Name	Case Name	Case No.
Slavensky, Ada Ann	Christian, Marilyn	14-cv-7542
Smitherman, Susan	Christian, Marilyn	14-cv-7542
Steinhilber, Barbara	Christian, Marilyn	14-cv-7542
Warner, Betty	Christian, Marilyn	14-cv-7542
Cohen, Deena	Cohen, Deena	14-cv-8060
Shull, Mary Frances	Shull, Mary Frances	15-cv-1595
Yenna, Annabelle	Yenna, Annabelle	15-cv-2081
Allen, Karen	Johnson, Mary	15-cv-2082
Cantu, Kathlene	Johnson, Mary	15-cv-2082
Caruss, Carol	Johnson, Mary	15-cv-2082
Clark, Susan	Johnson, Mary	15-cv-2082
Crowley, Betty	Johnson, Mary	15-cv-2082
Culver, Susan	Johnson, Mary	15-cv-2082
Dempley, Joan	Johnson, Mary	15-cv-2082
Deringer, Judy	Johnson, Mary	15-cv-2082
Dillabough, Elaine	Johnson, Mary	15-cv-2082
Harris, Kimain	Johnson, Mary	15-cv-2082
Hubel, Judy	Johnson, Mary	15-cv-2082
Ingram, Frances	Johnson, Mary	15-cv-2082
Johnson, Mary	Johnson, Mary	15-cv-2082

Plaintiff Name	Case Name	Case No.
Johnston, Kathy	Johnson, Mary	15-cv-2082
Kelly, Vickie	Johnson, Mary	15-cv-2082
Ludlow, Muriel	Johnson, Mary	15-cv-2082
Mason, Sandra	Johnson, Mary	15-cv-2082
Ostowari, Shahnaz	Johnson, Mary	15-cv-2082
Pell, Connie	Johnson, Mary	15-cv-2082
Sexton, Jeannie	Johnson, Mary	15-cv-2082
Thaler, Honi	Johnson, Mary	15-cv-2082
Vandenburg, Nancy	Johnson, Mary	15-cv-2082
Yee, Sue	Johnson, Mary	15-cv-2082
Zoppel, Gayle	Johnson, Mary	15-cv-2082
Nathanson, Ronnie Arlene	Nathanson, Ronnie Arlene	15-cv-3784
Baker, Jeannine	Hollis, Janela	15-cv-5503
Beadling, Carolyn	Hollis, Janela	15-cv-5503
Bird, Jean	Hollis, Janela	15-cv-5503
Carmen, Judith	Hollis, Janela	15-cv-5503
Chatham, Betty	Hollis, Janela	15-cv-5503
Edwards, Maria de Jesus	Hollis, Janela	15-cv-5503
Friedland, Shirley	Hollis, Janela	15-cv-5503
Goodburne, Joan	Hollis, Janela	15-cv-5503

Plaintiff Name	Case Name	Case No.
Graham, Patricia	Hollis, Janela	15-cv-5503
Hadley, Iva Sue	Hollis, Janela	15-cv-5503
Hardenbrook, Debbie	Hollis, Janela	15-cv-5503
Hillery, Mary	Hollis, Janela	15-cv-5503
Hollis, Janela	Hollis, Janela	15-cv-5503
Israel, Margaret	Hollis, Janela	15-cv-5503
Kieran, Carole	Hollis, Janela	15-cv-5503
Lachky, Lillian	Hollis, Janela	15-cv-5503
Lesaca, Paz	Hollis, Janela	15-cv-5503
Moran, Ruth	Hollis, Janela	15-cv-5503
Simpson, Rosemary	Hollis, Janela	15-cv-5503
Stutz, Don	Hollis, Janela	15-cv-5503
Schaffer, Gail	Schaffer, Gail	15-cv-5700
Penn, Frances	Penn, Frances	15-cv-6280
Hanrahan, Sioban	Hanrahan, Sioban	15-cv-6443
Buckingham, Julie Anne	Buckingham, Julie Anne	15-cv-6901
Armstrong, Donna	Moore, Mary	15-cv-7919
Blackwood, Debra	Moore, Mary	15-cv-7919
Boeh, June	Moore, Mary	15-cv-7919

Plaintiff Name	Case Name	Case No.
Dignan, Christine	Moore, Mary	15-cv-7919
Driscoll, Linda	Moore, Mary	15-cv-7919
Ferjutz, Nancy	Moore, Mary	15-cv-7919
Good, Angela	Moore, Mary	15-cv-7919
Lewis, Rosalind	Moore, Mary	15-cv-7919
Moore, Mary	Moore, Mary	15-cv-7919
Okon, Norma	Moore, Mary	15-cv-7919
Okonkwo, Rina	Moore, Mary	15-cv-7919
Rito, Connie	Moore, Mary	15-cv-7919
Romersa, Susan	Moore, Mary	15-cv-7919
Stallings, Emily	Moore, Mary	15-cv-7919
Wheeler, Joan	Moore, Mary	15-cv-7919
Aleikay, Mouloud	Aleikay, Mouloud	15-cv-8175
Bierschenk, Sharon	Bierschenk, Sharon	15-cv-8176
Walker, Marcia	Walker, Wendy (Estate of Marcia Walker)	15-cv-8178
Wobbeking, Kathleen	Wobbeking, Kathleen	15-cv-8179
Pearce, Barbara	Pearce, Barbara	15-cv-8225
Stewart, Devann	Stewart, Devann	16-cv-04197
Wiley, Patricia	Wiley, Patricia	16-cv-04927
Good, Angela	Good, Angela	16-cv-08028

Plaintiff Name	Case Name	Case No.
Teague, Marianna	Teague, Marianna	16-cv-08029
Ammon, Carol Ann	Ammon, Carol Ann	16-cv-1036
Conte, Arlene	Conte, Arlene	16-cv-2126
Hastings, Janet	Hastings, Janet	16-cv-2461
Rubin, Irene	Rubin, Irene	16-cv-2632
McClurkin, Jane	McClurkin, Jane	16-cv-3194
Stankewich, Stacey	Stankewich, Stacey	16-cv-4928
Kushnir, Mira	Kushnir Mira	16-cv-5998
Lee, Vivian	Lee Vivian	16-cv-6000
Armstrong, Donna	Rodgers, Linda	16-cv-695
Blackwood, Debra	Rodgers, Linda	16-cv-695
Byers, Renee	Rodgers, Linda	16-cv-695
Carmen, Judith	Rodgers, Linda	16-cv-695
Driscoll, Linda	Rodgers, Linda	16-cv-695
Ferjutz, Nancy	Rodgers, Linda	16-cv-695
Gardizi, Ramzia	Rodgers, Linda	16-cv-695
Good, Angela	Rodgers, Linda	16-cv-695
Hardenbrook, Debbie	Rodgers, Linda	16-cv-695
Harris, Jean	Rodgers, Linda	16-cv-695
Jenkins, Jeannie	Rodgers, Linda	16-cv-695

Plaintiff Name	Case Name	Case No.
Lachky, Lillian	Rodgers, Linda	16-cv-695
Lesaca, Paz	Rodgers, Linda	16-cv-695
Rauch, Lauren	Rodgers, Linda	16-cv-695
Rodgers, Linda	Rodgers, Linda	16-cv-695
Sklar, Zhanna	Rodgers, Linda	16-cv-695
Teague, Marianna	Rodgers, Linda	16-cv-695
Wheeler, Joan	Rodgers, Linda	16-cv-695
Odom, Charlotte S.	Odom, Charlotte	16-cv-696
Rito, Connie	Rito, Connie	17-cv-04207
Christie, Brenda	Christie, Brenda	17-cv-10146
Foster, Donna	Foster, Donna	17-cv-12328
Bierner, Barbara	Bierner, Barbara	17-cv-12865
Green-Harris, Joanne	Green-Harris, Joanne	17-cv-13121
Campbell, Mary Frances	Campbell, Mary Frances	17-cv-13580
Bryner, Lynda	Bryner, Lynda	17-cv-13712
Diemar, Judith	Diemar, Judith	17-cv-1600
Rhodes, Donna	Rhodes, Donna	17-cv-3419
Lavine, Audrey	Lavine, Audrey	17-cv-3727
Askanase, Susan	Askanase, Susan	17-cv-3816
Jones, Emy Jane	Jones, Emy Jane	17-cv-3817
Aldous, Elaine	Aldous, Elaine	17-cv-4565

Plaintiff Name	Case Name	Case No.
Fiormonte, Clareen	Fiormonte, Clareen	17-cv-5623
Davis, Peggy	Davis, Peggy	17-cv-5984
Patterson, Thelma	Patterson, Thelma	17-cv-690
Simpson, Rosemary	Simpson, Rosemary	17-cv-7400
Cooney, Pok	Cooney, Pok	17-cv-7401
Estes, Betty	Estes, Betty	17-cv-7402
Gardizi, Ramzia	Gardizi, Ramzia	17-cv-8357
Gamble, Melanie	Gamble, Melanie	17-cv-8379
Fairfield, Ruth	Fairfield, Ruth	18-cv-10945
Brown, Marilyn	Brown, Marilyn	18-cv-10974
Callahan, Deborah	Callahan, Deborah	18-cv-11374
McGarvey, Marcia	McGarvey, Marcia	18-cv-12127
Corriveau, Margaret	Corriveau, Margaret	18-cv-12536
Rosen, Keri	Rosen, Keri	18-cv-13386
Wiese, Ellen	Wiese, Ellen	18-cv-13908
Lachky, Lillian	Lachky, Lillian	18-cv-1408
Woods, Christine	Woods, Christine	18-cv-14989
Starsiak, Stephanie	Starsiak, Stephanie	18-cv-15194

Plaintiff Name	Case Name	Case No.
Brace-Carter, Brenda	Brace-Carter, Brenda	18-cv-15489
Carter, Martha	Carter, Martha	18-cv-15491
Maher, Frances	Maher, Frances	18-cv-1568
Jeanmard, Vivian Marie	Jieanmard, Vivian Marie	18-cv-15828
Sirat, Zhara	Sirat, Zhara	18-cv-1872
Kownacki, Betty	Kownacki, Betty	18-cv-1875
Friedland, Lois	Friedland, Lois	18-cv-1876
Stuchly, Philomina	Stuchly, Philomina	18-cv-2116
Grogan, Jan	Grogan, Jan	18-cv-4226
Guidry, Lynn	Guidry, Lynn	18-cv-8484
Lundwall, Barbara	Lundwall, Barbara	18-cv-8614
Day, Janet	Day, Janet	18-cv-942
Ashworth, Robbie	Ashworth, Robbie	19-cv-12239
Villafane, Ernestina	Villafane, Earnestina	19-cv-12804
Brown, Theresa	Brown, Theresa	19-cv-13410
Burkey, Janice	Burkey, Janice	19-cv-15698
Inscho, Som	Inscho, Som	19-cv-16015
Levi, Christine	Levi, Christine	19-cv-16017
Brockwell, Brenda	Brockwell, Brenda	19-cv-17271

Plaintiff Name	Case Name	Case No.
Fernandez, Zoraida	Fernandez, Zoraida	19-cv-17635
Stevens, Roberta	Stevens, Roberta	19-cv-17637
Nanfito, Rosanda	Nanfito, Rosanda	19-cv-19437
Hunter, Ruth	Hunter, Ruth	19-cv-19843
Hodge, Nina	Hodge, Nina	19-cv-9373
Ward, Jerry	Ward, Jerry	20-cv-08838
Jiang, Hong	Jiang, Hong	20-cv-1304
Gordon, Elvira	Gordon, Elvira	20-cv-3132
Wakeham, Karen	Wakeham, Karen	20-cv-7350
Weindruch, Donna	Weindruch, Donna	20-cv-8832
Strief, Gloria Joan	Strief, Gloria Jean	20-cv-9380
Gray, Patricia Dean	Gray, Patricia Dean	21-cv-11766
Valdez, Rayline	Valdez, Rayline	21-cv-11779
Hovdet, Iona	Hovdet, Iona	21-cv-11793
Freiberg, Margaret	Freiberg, Margaret	21-cv-11798
Mika, Rosemarie	Mika, Rosemarie	21-cv-6950