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)

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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

[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.*).

appears on the labels of prescription drugs that are marketed in the United States."[2] *Id.* at 303.

"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,

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[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 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).

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, "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 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).

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

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 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

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

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.*

"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.)

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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).

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 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:

[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.

> 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.

(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.)

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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*

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] 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,

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§ 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").)

> 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

[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.

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 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.

[11] The Court further stated that the "Plaintiffs did not present any evidence at trial to refute preemption." *Glynn*, 951

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

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.

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.*

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

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

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 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 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.

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 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.

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

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.)

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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

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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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. at 318

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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,*

(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

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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 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.

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 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]

[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").

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 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

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 …

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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.)

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

[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.

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.

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. 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**

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

> **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 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)).)

[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)).)

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 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

[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

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 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.

Merck's Prior Approval Supplement must have been because of 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. Merck must

[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, ---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

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.*

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

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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.

manufacturer to comply with both federal and state law.[27] The "possibility" that the Letter communicated a conflict between

[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 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

federal and state law "is not enough."[28] *Albrecht*, 587 U.S. at 314 (cleaned up). Although it is possible that, had Merck

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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

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

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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 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.

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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[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

[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.

§ 355(o)(4)(A) does not "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." *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

[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.

maintain its label in accordance with existing requirements[.]"). Thus, since the FDA had not 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] (*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

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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 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.

(J.A. at 1280.)

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.

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.