No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari
To The United States Court of Appeals
For The Third Circuit

BRIEF FOR PETITIONER

STEPHANIE PARKER
JONES DAY
1420 Peachtree St., NE
Suite 800
Atlanta, GA 30309

BENJAMIN M. FLOWERS
JONES DAY
325 John H. McConnell Blvd.
Suite 600
Columbus, OH 43215

SHAY DVORETZKY
Counsel of Record
YAAKOV M. ROTH
JEFFREY R. JOHNSON
JONES DAY
51 Louisiana Ave., NW
Washington, DC 20001
(202) 879-3939
sdvoretzky@jonesday.com

Counsel for Petitioner

QUESTION PRESENTED

In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court held that the FDA's approval of a drug label does not, standing alone, insulate the manufacturer from failure-to-warn liability under state tort law. At the same time, the Court recognized that if "the FDA would not have approved" the label demanded by state law, then the manufacturer could invoke an "impossibility" preemption defense. *Id.* at 571.

In this case, it was "undisputed" that (i) "the FDA was aware of the possible link" between petitioner's drug and the risk at issue; (ii) petitioner "submitted a comprehensive safety update to the FDA reporting … numerous studies" finding "such an association"; (iii) petitioner "proposed warning language" about this risk, but the FDA "rejected" it; (iv) the FDA stated that the "conflicting nature of the literature d[id] not provide a clear path forward" and that it needed "more time" to consider "the issue of a precaution"; and (v) only later, after a report from a task force, did the FDA become "confident" that an association "potentially" existed. Pet.App.59a–60a.

The Third Circuit nonetheless held that a jury could find that petitioner had not shown by "clear and convincing evidence" that the FDA would have rejected a warning label of the type that respondents claim state law required. *See* Pet.App.37a, 56a–57a.

The question presented is: Is a state-law failure-to-warn claim preempted when the FDA rejected the drug manufacturer's proposal to warn about the risk after being provided with the relevant scientific data; or must such a case go to a jury for conjecture as to *why* the FDA rejected the proposed warning?

PARTIES TO THE PROCEEDING AND RULE 29.6 STATEMENT

Petitioner is Merck Sharp & Dohme Corporation, a wholly owned subsidiary of the entity formerly known as Schering Plough Corporation, which has been renamed Merck & Co., Inc. No publicly held corporation owns 10% or more of the stock of Merck & Co., Inc.

Respondents, listed in Appendix B, are more than five hundred plaintiffs who brought state-law failure-to-warn claims against Merck, alleging that they were injured by Merck's drug Fosamax prior to September 14, 2010. The Third Circuit resolved their appeals in one consolidated opinion. Pet.App.1a n.*. Pursuant to this Court's Rule 12.4, Merck filed a consolidated petition to challenge the Third Circuit's decision.

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INTRODUCTION

Merck told the FDA what it knew about the link between its drug Fosamax and the risk of atypical femoral fractures; Merck filed a formal request seeking FDA approval to add a warning to Fosamax's label addressing this risk; and the FDA rejected that request. In *Wyeth v. Levine*, this Court recognized that a pharmaceutical manufacturer cannot be held liable under state law for failure to warn about a health risk if the FDA would not have permitted the manufacturer to add that warning to its federally regulated label. 555 U.S. 555, 572–73 (2009). But unlike in *Levine*, here there is no need to guess what would have happened in a counterfactual world. It is clear that the FDA *would not* have allowed Merck to warn about the risk at issue because the FDA *did not* allow Merck to warn about it.

The Third Circuit nonetheless concluded that the preemption defense must be put to a jury—to decide as a counterfactual matter, while applying a unique, heightened standard of proof, whether the FDA might have approved a warning had Merck phrased it differently. That is misguided. The FDA's final agency action controls the preemption inquiry here as a matter of law. There is no room under either the Supremacy Clause or the federal drug labeling laws to speculate about *why* the agency blocked compliance with the alleged state-law duty.

Focusing on the meaning and scope of the FDA's actual decision also simplifies a set of related procedural questions that bogged down the Court of Appeals. Construing an agency's action is a question of law for the court to decide, not a factual dispute for a jury. And it does not implicate evidentiary

burdens of proof, which so concerned the Third Circuit. When, as here, the FDA has spoken by refusing to allow a warning (and there is no evidence it lacked any material information), a court must dismiss any state failure-to-warn claims as legally preempted.

OPINIONS BELOW

The district court's opinion granting judgment to petitioner, Pet.App.113a–52a, appears at 2014 WL 1266994. The Third Circuit's decision vacating and remanding, Pet.App.1a–95a, was reported at 852 F.3d 268.

JURISDICTION

The Third Circuit entered judgment on March 22, 2017, and denied petitioner's timely petition for rehearing on April 24, 2017. *See* Pet.App.1a, 175a–76a. Justice Sotomayor extended the time to file a certiorari petition until August 22, 2017, *see* No. 16A1264, on which day Merck filed. This Court has jurisdiction under 28 U.S.C. § 1254(1).

PROVISIONS INVOLVED

Relevant statutory and regulatory provisions are reproduced in Appendix A.

STATEMENT

A. Statutory and Regulatory Framework.

1. Labeling is the "centerpiece" of the FDA's "risk management" strategy for prescription drugs, and the primary method by which it communicates its conclusions about when and how drugs can be safely used. FDA, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934

(2006). Because of labeling's central role, the FDA has final say over a prescription drug's label throughout the drug's lifespan.

Before a new, brand-name drug can be approved, the manufacturer must submit "specimens of the labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1). (Generic drugs must use the label approved for the brand-name version. *Id.* § 355(j)(2)(A)(v).) The FDA uses those submissions when deciding whether the drug is "safe for use under the conditions prescribed, recommended, or suggested" in its "labeling." *Id.* § 355(d).

2. "Despite the rigorous steps in the process" of approving a drug, "the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime." FDA, *Step 5: FDA Post-Marketing Drug Safety Monitoring* (Jan. 4, 2018), https://perma.cc/QU75-KDAC. Both the manufacturer and the FDA have roles to play in ensuring that a drug's label evolves alongside its risk profile.

a. The manufacturer must ensure that the label adequately warns of the drug's risks in light of new evidence. *See Levine*, 555 U.S. at 570–71 ("[T]he manufacturer bears responsibility for the content of its label at all times."). So the manufacturer must seek to revise its label "as soon as" the evidence justifies a change. 21 C.F.R. § 201.57(c)(6)(i); *see also id.* § 201.57(c)(7). A manufacturer may discharge this duty in one of two ways. But, either way, the FDA reviews the proposed label under the same regulatory standard, and "retains authority to reject" the manufacturer's proposed "labeling changes." *Levine*, 555 U.S. at 571.

First, through the so-called "Changes Being Effected" (or "CBE") process, a manufacturer may revise the label and begin distributing the relabeled product immediately upon submitting an application requesting FDA approval. This process is available "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling" under the FDA's regulatory standards. 21 C.F.R. § 314.70(c)(6)(iii)(A). But if the FDA ultimately rejects the application, it may "order the manufacturer to cease distribution" of the drugs already "made with the manufacturing change." *Id.* § 314.70(c)(7).

Second, manufacturers may seek the agency's advance permission by submitting a Prior Approval Supplement, or "PAS." "Historically," the FDA has "accepted PAS applications instead of CBE supplements," "particularly where significant questions exist on whether to revise or how to modify existing drug labeling." U.S. Cert. Br. 5. Thus, "in practice, manufacturers typically consult with FDA prior to adding risk information to labeling," 71 Fed. Reg. at 3934, to avoid the waste and confusion that would otherwise result if the FDA later disapproved the changes. As with CBE applications, the FDA will reject a manufacturer's PAS if it concludes that the proposed changes do "not comply with the requirements for labels" in the applicable regulations. 21 C.F.R. § 314.125(b)(6), (b)(8).

b. Although drug manufacturers bear primary responsibility for their own labels, the FDA

also has its own statutory obligation to ensure that warning labels are complete, correct, and up-to-date.

Under statutory amendments that took effect in 2007—after the events at issue in *Levine*, but before those at issue here—if the FDA "becomes aware of new safety information that … should be included in the labeling of the drug," then the agency "shall promptly notify" the manufacturer. 21 U.S.C. § 355(*o*)(4)(A). Then, the manufacturer must either "submit a supplement proposing changes to the approved labeling to reflect the new safety information" or explain why it "does not believe a labeling change is warranted." *Id.* § 355(*o*)(4)(B).

If the FDA "disagrees" with the manufacturer's response, it "shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes." *Id.* § 355(*o*)(4)(C). Of course, the FDA has the final say in those discussions; it "may issue an order directing [the manufacturer] to make such a labeling change as [it] deems appropriate to address the new safety information." *Id.* § 355(*o*)(4)(E); *cf.* § 355(*o*)(4)(F) (appeals process).

Consistent with its statutory obligation, the FDA works cooperatively with manufacturers when they seek approval for new drugs or revised labeling. Throughout the approval process for new drugs, the FDA "communicate[s] with applicants about scientific, medical, and procedural issues that arise." 21 C.F.R. § 314.102(a). If it spots "easily correctable deficiencies," it will "make every reasonable effort to communicate" those deficiencies "promptly," so as "to permit the applicant to correct" them "relatively

early in the review process." *Id.* § 314.102(b). Similarly, "if the only deficiencies in [an application] concern editorial or similar minor deficiencies in the draft labeling," the "FDA will approve" the application "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." *Id.* § 314.105(b).

The FDA applies the same principles to supplemental applications submitted through the CBE and PAS processes. *See* 21 C.F.R. § 314.71(b), (c); U.S. Cert. Br. 5. If the agency agrees that a label revision is warranted, it will work with the manufacturer to develop appropriate language. *See* U.S. Cert. Br. 5–6, 21–22. But if the FDA concludes that the proposed warning is scientifically unjustified, it will deny the applicant's request in a "complete response letter." 21 C.F.R. § 314.110(a). That letter generally "describe[s] all of the specific deficiencies that the agency has identified" in the application and, "[w]hen possible," "will recommend actions that the applicant might take to place the application … in condition for approval." *Id.* § 314.110(a)(1), (a)(4); *see also* U.S. Cert. Br. 5–6.

B. Fosamax and Its Label.

1. In healthy bone tissue, new bone cells slowly replace old ones. *See* Liza J. Raggatt & Nicola C. Partridge, *Cellular and Molecular Mechanisms of Bone Remodeling*, 285 J. Biological Chem. 25103, 25103–07 (2010). In some post-menopausal women, that process falters: more bone is removed than is replaced, leaving less dense bones that are more likely to break. *See* Pet.App.5a. This altered process can lead to osteoporosis.

In 1995, the FDA approved alendronate—better known as Fosamax, a Merck product—to treat osteoporosis in postmenopausal women. Pet.App.12a. Fosamax is a type of bisphosphonate, a class of drugs that slow down the removal of old bone cells. In this way, it maintains the balance between removal and replacement and helps patients retain bone mass. "Solid evidence" demonstrates that Fosamax "decreas[es] the risk of vertebral fracture (by 40% to 70%), hip fractures (by 20% to 50%), and nonvertebral fractures (by 15% to 39%)." Robert A. Adler, et al., *Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research*, 31 J. Bone & Mineral Research 16, 16–17 (2015).

But the mechanism that makes Fosamax a success—the way it slows down bone removal—could theoretically increase the risk of other fractures. Some have hypothesized that bisphosphonates "may inhibit microdamage repair by preventing … bone resorption at the sites of microdamage," creating small cracks that might then progress into more serious fractures. Pet.App.12a.

2. Merck has long worked with the FDA to ensure that Fosamax's label adequately warns of its risks. In 1992, Merck brought the theoretical considerations mentioned above to the FDA's attention during the approval process. The agency approved Fosamax's label without requiring any mention of this hypothetical risk. Pet.App.12a–13a. Merck then continually provided the FDA with updates about the data, adverse events, and literature available after Fosamax reached the

market. Pet.App.13a ("Merck kept the FDA informed of … studies suggesting a possible association between bisphosphonates and fractures.").

Over time, evidence began to emerge that a very small percentage of long-term bisphosphonate users—and some non-users—suffered from what later came to be known as atypical femoral fractures. To understand these fractures, it helps to understand the nomenclature sometimes used (although inconsistently) to describe different types of bone injuries. Traumatic fractures result from the application of extraordinary force to a bone, and low-energy fractures occur absent such force. Certain low-energy fractures are sometimes called "stress fractures" or "insufficiency" fractures. *See* Richard H. Daffner & Helene Pavlov, *Stress Fractures: Current Concepts*, 159 Am. J. Radiology 245, 245–46 (1992); U.S. Cert. Br. at 8 n.7.

Atypical femoral fractures are low-energy fractures that occur in the long shaft of the femur (the "diaphyseal" region) or in the portion below the part of the femur that forms the hip (the "subtrochanteric" region). In March 2008, Merck provided the FDA with a periodic safety update that included "over 30 pages of information regarding" these fractures. Pet.App.14a. Merck also noted that "[r]ecent publications" "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures." Pet.App.14a. Shortly afterwards, Merck sent the FDA a copy of a letter in the New England Journal of Medicine that provided additional "evidence of a potential link between [prolonged] alendronate use and low-energy

fractures of the femur." Brett A. Lenart, et al., *Atypical Fractures of the Femoral Diaphysis in Postmenopausal Women Taking Alendronate*, 358 New England J. Med. 1304, 1305 (Mar. 20, 2008); *see* Pet.App.14a.

In June 2008, the FDA told Merck that it was "aware of reports regarding" atypical femoral fractures "in patients using bisphosphonates," and cited several of the key articles. J.A.280–81. It asked Merck and other bisphosphonate manufacturers for more information about this "developing safety signal." J.A.280. Merck "promptly complied." Pet.App.14a.

3. While the FDA was "analyzing Merck's data," Merck sought approval to revise Fosamax's label to include the risk of atypical femoral fractures. Pet.App.14a. Merck submitted PASs requesting revisions to Fosamax's labels to address "low-energy fractures that have been reported, of which some ha[d] been stress/insufficiency, at the subtrochanteric region of the femoral shaft." J.A.670. Merck acknowledged that it was not possible "to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures." *Id.* But Merck still "believe[d] that it [wa]s important to include an appropriate statement about them in the product label," given their "clinical importance" and "their temporal association with bisphosphonate use." *Id.*

In particular, Merck sought to revise two sections of Fosamax's labels: the Adverse Reactions section and the Warnings and Precautions section. To include an adverse event in the Adverse Reactions

section, there must be "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7). Merck proposed adding "low-energy femoral shaft fracture" to the Fosamax label's "Adverse Reactions" section. Pet.App.16a.

Merck also sought to revise the Warnings and Precautions part of the label. For that, the causal link between the drug and an adverse reaction must be more certain—there must be "reasonable evidence of a causal association with a drug." 21 C.F.R. § 201.57(c)(6)(i). In addition, the Warnings and Precautions section is reserved for adverse reactions that are more clinically significant than those listed only in the Adverse Reactions section of the label. *See* FDA, *Supplemental Applications Proposing Label Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49603, 49605–06 (2008) (FDA's standard is designed to "prevent overwarning" so that less important information does not "overshadow more important warnings"); U.S. Cert. Br. 3.

Merck sought to revise this section of Fosamax's labels to state:

> 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.

Pet.App.15a–16. In the accompanying materials, Merck described the reports that it had received of "low-energy subtrochanteric/femoral shaft fractures," J.A.748, identified numerous studies addressing the subject, J.A.757–61, and explained its chosen terminology, J.A.746.

4. The FDA responded in a complete response letter issued on May 22, 2009. J.A.510–13. It "agree[d] that atypical and subtrochanteric fractures should be added to the ADVERSE REACTIONS" portion of Fosamax's labels. J.A.511. It "recommend[ed]" a minor change to Merck's drafting, suggesting that Merck add "low energy femoral shaft *and subtrochanteric* fractures" (rather than just

"low-energy femoral shaft fractures"). J.A.512 (emphasis added).

As for the Warnings and Precautions section, however, the FDA rejected Merck's request, and cited the following "reasons":

> [Y]our 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.511–12.

The FDA's split decision—rejecting a warning about atypical femoral fractures while approving an addition to Fosamax's Adverse Reactions label about the very same risk—tracked Merck's back-and-forth with agency officials. In April 2009, the FDA official who later authored the complete response letter told Merck that the agency could "agree to add language in the Adverse Reactions section," but that Merck's "elevation of the issue to a precaution" was "prolonging review," as "the conflicting nature of the literature d[id] not provide a clear path forward." Pet.App.17a. Later, another FDA official similarly told Merck by email that its "currently pending" PASs "could be approved at this time only for inclusion of the atypical fracture language proposed in the postmarketing adverse events section," but "[i]f Merck agree[d] to hold off on the W&P language

at this time," the FDA could "close out th[o]se supplements" and then "work with … Merck to decide on language for a W&P atypical fracture language, if it is warranted." J.A.508.

In June 2009, Merck issued new labels implementing the FDA's revisions to its Adverse Reactions proposal. J.A.274, 279.

5. The FDA continued to review the possible relationship between bisphosphonates and atypical femoral fractures. In a March 2010 Drug Safety Communication, the FDA explained that "the data ... reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." J.A.519; *see also* J.A.520 (discussing how FDA's analysis of manufacturers' data "did not show an increase in [the risk of atypical femoral fractures] in women using these medications"); J.A.520 (discussing a December 2008 study that showed "similar numbers of atypical subtrochanteric femur fractures" regardless of use of bisphosphonates). The FDA therefore advised doctors to "[b]e aware" of this issue, but to "[c]ontinue to follow the recommendations in the [unrevised] drug label." J.A.521. The FDA also explained that it was "working closely with outside experts," including those from a task force assembled by the American Society of Bone and Mineral Research, "to gather additional information that may provide more insight into this issue." J.A.519–20.

The task force published its first report in September 2010. It noted that "[t]he radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures."

Elizabeth Shane, et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research*, 25 J. of Bone & Mineral Research 2267, 2270 (2010) ("*First Report*"); *see also* Elizabeth Shane, et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research*, 29 J. of Bone & Mineral Research 1, 10–12 (2014) (later concluding that the "evidence suggests that [atypical femoral fractures] are stress fractures"). The task force crafted a "provisional case definition" of the "features for complete and incomplete atypical [femoral] fractures," and it reassessed prior studies in light of that definition. *First Report*, 25 J. of Bone & Mineral Research at 2268–69. The task force concluded that "a causal association between [bisphosphonates] and atypical fractures ha[d] not been established." *Id.* at 2267. Nonetheless, because "recent observations suggest[ed] that the risk rises with increasing duration of exposure," the task force recommended that "[p]hysicians and patients should be made aware of the possibility of atypical femoral fractures." *Id.*

6. The FDA responded immediately. It explained that the task force's case definition would "help greatly in identifying cases and reporting on them, and should facilitate future studies" assessing any causal link between "these unusual fractures" and bisphosphonate use. J.A.523. The FDA also recognized that the task force "recommended changes to product labels," which the agency was

"considering" as part of its "thorough[] review[]" of "all long term data available." J.A.524–25.

A month later, the FDA announced that, "[a]lthough it is not clear if bisphosphonates … cause" atypical femoral fractures, information about them would be "added to the *Warnings and Precautions* section of the labels of all bisphosphonate[s]." J.A.246, 247. The Deputy Director of the Office of New Drugs, an FDA official, explained that the task force's report "helped to clarify the features of atypical femur fractures" and "provide[d] more information that more closely associate[d] these atypical fractures with long-term bisphosphonate use." J.A.488–89. That is, the task force's report "really helped" the agency conclude that atypical femoral fractures are "something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for." J.A.494.

Citing both the task force report and its duties under section 355(*o*)(4), the FDA wrote to Merck to propose changes to the Warnings and Precautions section of Fosamax's labels. J.A.526–34. Merck responded with suggested revisions, including "to make clear that doctors should attempt to rule out stress fractures," so that complete fractures could be avoided. Pet.App.22a. Although the FDA accepted some of Merck's proposed changes, it rejected Merck's stress-fracture-related ones, noting the agency's belief that, "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." J.A.566. "In addition, the risk factors listed in

the proposed changes have not been sufficiently validated to include in the labeling at this time." *Id.* Merck revised Fosamax's labels according to the FDA's instruction. Pet.App.23a.

C. This Litigation.

1. After Merck changed its label, many Fosamax users who had allegedly suffered atypical femoral fractures sued. They generally alleged that Merck failed to warn about this risk. Pet.App.23a–24a. Over a thousand cases were sent to a multi-district litigation proceeding in the District of New Jersey. Pet.App.23a. The District Court litigated several bellwether cases—with *Glynn v. Merck Sharp & Dohme Corp.*, No. 11:cv-05304 (D.N.J.), being the first to proceed to trial—to see whether those cases could resolve any issues pertinent to the other thousand-plus cases. Pet.App.115a.

Federal preemption was one such global issue. Drug manufacturers may not be held liable under state tort law if the FDA prevented or would have "prevented [them] from adding a stronger warning." *Levine*, 555 U.S. at 573; *see also id.* at 571 (rejecting Wyeth's preemption defense because it lacked "clear evidence that the FDA" would have rejected a stronger warning). From the beginning, Merck told plaintiffs and the District Court that preemption would be critical to its defense, and the various parties conducted discovery into Merck's dealings with the FDA accordingly. *See* Pet.App.116a.

After discovery, Merck moved for summary judgment in *Glynn*, arguing that the claims were preempted by the FDA's rejection of Merck's proposed warning. Pet.App.116a. But the District

Court wanted to resolve the issue based on a full record, so it allowed the case to proceed to trial. Pet.App.116a. After trial, the District Court granted Merck's motion. Pet.App.168a. It recognized that impossibility preemption "'is a demanding defense.'" Pet.App.168a (quoting *Levine*, 555 U.S. at 573). It nevertheless concluded that there was "clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label" before the September 2010 task force report. *Id.*

"Throughout the entire pre-trial, trial, and post-trial proceedings in *Glynn*, the [District Court] made it clear that … it wanted the parties to introduce any and all relevant evidence [regarding preemption] because of the effects it could have on the MDL as a whole." Pet.App.124a; *see also* Pet.App.124a–129a (detailing the court's efforts). The District Court followed through by ordering plaintiffs whose alleged injuries occurred before the task force's report to show cause why their claims were not preempted like Glynn's. Pet.App.129a–30a. After thus providing these plaintiffs with yet another "opportunity to identify genuine issues of material fact" on that issue, Pet.App.136a, the District Court held their claims preempted. Pet.App.152a. It also found that some of the plaintiffs' other claims were failure-to-warn claims in disguise, and thus preempted for the same reason. Pet.App.139a–46a.

2. The Third Circuit vacated and remanded. It first held that *Levine*'s reference to "clear evidence" created a heightened standard of proof: to prevail on a preemption defense, "[t]he 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,'" which the court equated with the more familiar "clear-and-convincing-evidence" standard. Pet.App.35a–36a, 37a. According to the Third Circuit, the defendant must prove it is "*highly probable*" that the FDA would have rejected the change. Pet.App.37a (emphasis added).

The court also held that whether the FDA would have rejected the proposed change is a jury question, even when the historical facts are undisputed, because the inquiry is "counterfactual." Pet.App.54a. A manufacturer thus cannot establish the preemption defense as a matter of law, pre-trial, absent a "'smoking gun' rejection letter from the FDA" that would leave a jury no choice but to find the state-law claim preempted. Pet.App.55a.

Applying that framework, the Third Circuit found no smoking gun here. It acknowledged the considerable strength of Merck's position. Prior to the task force report, the FDA had repeatedly expressed doubt about the evidence tying bisphosphonate use to atypical femur fractures, including in rejecting Merck's proposed warning. Pet.App.59a–61a. To prevail, respondents would have to persuade juries to overlook this evidence and to conclude that the FDA spurned Merck's proposal not because it doubted the underlying data or need for a warning, but for some other, curable deficiency that it refused to help Merck resolve. In other words, respondents would have to prove that the FDA chose to leave patients uninformed rather than working with Merck on acceptable language. Pet.App.61a–62a.

Although the court did not "discount the force of [Merck's] evidence," it concluded that a jury could still find it less than "highly probable" that the FDA would have rejected a label change had Merck simply phrased it differently. Pet.App.62a–63a. In its view, a jury could interpret the statements and actions of a federal regulatory authority and conclude that the FDA's rejection was all about Merck's terminology (for example, its use of the term "stress fractures"), and that the agency had flatly rejected the proposal for that reason rather than offer alternative language (as the law commands it to do). Pet.App.67a. Thus, "a reasonable jury applying a heightened standard of proof *could* conclude" that the FDA would have allowed a label change. Pet.App.67a. The Third Circuit therefore remanded the claims for trial (including the disguised failure-to-warn claims, which had been dismissed by the District Court on derivative grounds). Pet.App.74a.

3. Merck petitioned for certiorari. The Court called for the views of the Solicitor General. *See* 138 S. Ct. 533 (2017) (mem.). In response, the United States made two critical points.

First, the United States explained that the FDA does not reject scientifically justified warnings because of disagreement with a manufacturer's phrasing. *See* U.S. Cert. Br. 5–6, 21–22. To do so would be inconsistent with the FDA's own regulations. *See* U.S. Cert. Br. 5–6, 21; *supra* pp. 5–6. It would also violate the agency's statutory obligation to work with manufacturers on revised labeling. *See supra* pp. 4–5; U.S. Cert. Br. 22.

Second, the United States explained that the FDA's actions surrounding Fosamax reflected that

general approach. That is, the FDA rejected Merck's particular proposal because of "the agency's determination that the data was then insufficient to justify such a warning." U.S. Cert. Br. 19. That reasoning was set forth in the FDA's complete response letter, which stated that Merck's "justification for the proposed … language was inadequate." U.S. Cert. Br. 20 (emphasis omitted). It was not until "October 2010—after [the] task force['s] report"—that the FDA "came to 'believe that the information' about atypical femoral fractures should be added to the Warnings and Precautions section and therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax and other bisphosphonates." U.S. Cert. Br. 22 (quoting J.A.527).

SUMMARY OF ARGUMENT

If a manufacturer proposes to warn about a risk, discloses what it knows about that risk, and gets rebuffed by the FDA, failure-to-warn claims against it are preempted as a matter of law.

I. States may not require what federal law forbids. Accordingly, state tort law may not penalize drug manufacturers for failing to revise their labels in ways that federal law would not have allowed. It follows that, where the FDA rejects a manufacturer's proposal to warn about a disclosed risk, failure-to-warn claims premised on that risk are preempted.

A. In *Levine*, the Court acknowledged that, if the FDA would have prevented a manufacturer from revising its label as state law supposedly demanded, state-law claims premised on its failure to revise its label would be preempted. *See* 555 U.S. at 571–72.

In that case, however, the manufacturer could not make such a showing. It never tried to warn about the risk in question and was never "prohibited from doing so by the FDA." *Id.* at 572. Indeed, it did not even "suppl[y] the FDA with an evaluation or analysis" about that risk, and could not prove that the FDA "gave more than passing attention" to it. *Id.* at 572–73. Absent "clear evidence" that the FDA would have rejected the warning plaintiffs claimed state law required, state-law failure-to-warn claims against it could proceed. *Id.* at 571.

In two later cases, however—*PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), and *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013)—this Court explained that plaintiffs cannot avoid preemption through mere speculation about how a manufacturer could comply simultaneously with both state and federal law. In *Mensing*, the plaintiffs sued defendants that, as generic manufacturers, could not change their own labels. The Court held that even if the manufacturers might have been able to convince the FDA to change the brand-name drug's label, such "conjecture[]" does not "suffice to prevent federal and state law from conflicting for Supremacy Clause purposes." 564 U.S. at 621. And in *Bartlett*, this Court held that the mere possibility that the manufacturer could simultaneously "comply" with state and federal law by withdrawing from the market could not defeat preemption either. *See* 570 U.S. at 489–90.

B. These cases establish that failure-to-warn claims are preempted if a manufacturer proposes to warn about a risk, discloses the relevant information, and is turned back. In such situations,

it is impossible to comply with both state and federal law: the FDA "*would not* have approved a change" to the label, *Levine*, 555 U.S. at 571 (emphasis added), where the FDA *did not* approve a change to the label.

The applicable statutory and regulatory regime further demonstrates that the FDA's rejection of a proposal ends the matter. The FDA now has a statutory obligation to respond to new safety information by working with a manufacturer toward—or ordering a manufacturer to implement—appropriate revisions. *See* 21 U.S.C. § 355(*o*)(4). And the FDA's own regulations require it to correct poorly phrased or otherwise procedurally flawed but scientifically justified warnings, not to leave patients in the dark. The FDA's rejection of a proposed warning thus reflects its conclusion that no warning should be given. State tort law cannot second-guess that conclusion.

C. Respondents' failure-to-warn claims are preempted under these straightforward principles. Merck "kept the FDA informed" about the "possible connections" between bisphosphonate use and atypical femoral fractures. Pet.App.13a. Merck then sought to "add language to the … Warnings & Precautions … section[] of [Fosamax's] label" to address "atypical femoral fractures." Pet.App.15a. But the FDA rejected that request, reasoning that Merck's "justification" was "inadequate." J.A.511. Respondents' failure-to-warn claims are therefore preempted, because it was impossible for Merck to revise its label as they demand.

II. The Third Circuit reached a contrary conclusion because, in its view, a rational jury "could find it less than highly probable" that the FDA would

have rejected a *differently phrased* warning about atypical femoral fractures. Pet.App.56a–57a. Its conclusion reflects a basic misunderstanding of the regulatory regime and this Court's precedents.

A. The Third Circuit treated the relevant question as counterfactual. Rather than focusing on the FDA's actual decision, it asked what the FDA would have done had Merck proposed a different warning. That approach was mistaken in circumstances like these. Where the FDA has flatly rejected a manufacturer's request to add a warning, that rejection says everything one needs to know about whether the manufacturer could have complied with state and federal law.

In *Levine*, the Court *had* to inquire into what would have happened had Wyeth proposed a warning, because Wyeth had not in fact done so. There was no agency action directly addressing the health risk in question. That says nothing about the proper approach in a case like this one, where the manufacturer tried to provide a warning and the FDA said no.

Nor would speculation about what might have happened had Merck rephrased its proposal lead to a different result. The FDA does not disregard its statutory and regulatory duties and leave patients in the lurch when manufacturers propose scientifically justified warnings but need editorial assistance in articulating them. The contrary notion—advanced by respondents and credited by the Third Circuit—runs headlong into the presumption of regularity, not to mention the well-established principle that speculation may not defeat preemption.

B. Once one recognizes that what matters is what the FDA did with Merck's actual proposal—not ill-advised conjecture about what it might have done with a different one—the Third Circuit's related errors become apparent.

For example, the Third Circuit concluded that its hypothetical question presents a question of fact. But the real question here—the meaning and effect of the FDA's actual action—presents an obvious question of law, as all parties agree. Similarly, the Third Circuit concluded that its hypothetical question belonged to the jury rather than the judge. But questions of law must be resolved by a judge, not by a thousand different juries deciding individual cases. Finally, the Third Circuit concluded that manufacturers must prove what the FDA would have done by clear and convincing evidence. But questions of law are resolved without reference to such burdens of proof.

Even if the Third Circuit's general approach to the preemption question were correct, its answers to these related questions would be wrong. Whether or not the FDA would have approved a differently worded proposal is a fundamentally legal question about how the FDA would have applied its regulations in the context of an undisputed record of scientific data, not (as the Third Circuit seemed to think) an unbounded psychoanalysis of agency officials and their motives. And even if the Third Circuit's hypothetical question presents a question of fact, manufacturers need not make their case by clear and convincing evidence. Absent a statutory command, courts generally reserve such a heightened standard for truly compelling interests—

stripping parental rights, involuntarily committing the mentally ill, and the like. The tort suits here do not present such interests. And nothing in *Levine*—which used the phrase "clear evidence" only once, in passing—holds otherwise.

III. Finally, even if the law were exactly as the Third Circuit believed, Merck would still prevail here. The FDA's brief to this Court removes any possible doubt that, before October 2010, Merck could not have warned of the risk of atypical femoral fractures. The FDA has now declared that it rejected Merck's warning because of "the agency's determination that the data was then insufficient to justify such a warning," not because of concerns about Merck's "proposed text." U.S. Cert. Br. 19. The agency has also declared that it did not believe the data justified a warning about atypical femoral fractures until "October 2010," after the task force report. U.S. Cert. Br. 22.

No rational juror could get past this evidence, even applying a heightened burden of proof. To conclude otherwise, this Court would have to disregard the deference owed to an agency's explanation of its decision. And it would also have to ignore the record in this case, which supports the agency's current explanation of its decision at every turn. Because the FDA itself has now provided the very "smoking gun" the Third Circuit demanded, respondents' claims must fail.

Nonetheless, because of the practical importance of these recurring legal issues in ongoing pharmaceutical litigation across the nation, this Court should address the broader issues raised in this case.

ARGUMENT

I. WHEN THE FDA REJECTS A MANUFACTURER'S PROPOSAL TO WARN ABOUT A DISCLOSED RISK, THE MANUFACTURER CANNOT BE PENALIZED FOR FAILING TO WARN OF THAT RISK.

The Supremacy Clause says: "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof … shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. Simply put, "where state and federal law directly conflict, state law must give way." *Wos v. E.M.A. ex rel. Johnson*, 568 U.S. 627, 636 (2013). And federal law "directly conflicts" with state law when it is "impossible for a private party to comply with both state and federal requirements." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990); *see also Levine*, 555 U.S. at 589–90 (Thomas, J., concurring in the judgment). Consequently, courts may not enforce state laws that require what federal law forbids, or forbid what federal law requires.

As explained below, a state may not impose tort liability on a drug manufacturer for failing to warn of a risk that the FDA would not have permitted the manufacturer to warn about. Under those circumstances, the state would be penalizing a party for not taking action that federal law forbade. And when, as here, the FDA *rejected* a request by the manufacturer to warn of the risk, there is no doubt that state failure-to-warn claims are preempted. Indeed, it is hard to imagine a more obvious case of impossibility preemption.

A. Failure-To-Warn Claims Are Preempted If Federal Law Would Have Forbidden the Manufacturer To Revise Its Label.

This Court has considered preemption in the specific context of pharmaceutical labeling in a trio of recent decisions: *Levine*, *Mensing*, and *Bartlett*. Read together, these cases establish that a state may impose failure-to-warn liability only if the FDA would not have stood in the way of the manufacturer's warning about the risk at issue.

1. In *Levine*, the plaintiff successfully argued to the Vermont state courts that the label for Wyeth's drug Phenergan should have more strongly advised doctors to administer the drug indirectly through IV-solution (the "IV-drip" method) rather than directly into the vein (the "IV-push" method). 555 U.S. at 560–63. Wyeth argued in this Court that the "FDA's approvals" of Phenergan's label categorically created "a complete defense" to the tort claims. *Id.* at 558–59. In Wyeth's view, "it would have been impossible for it to comply with the state-law duty to modify Phenergan's labeling without violating federal law," *id.* at 563, because it had no power to change its label without FDA's permission.

This Court rejected Wyeth's claim of impossibility. It agreed in principle that, if federal law had prevented Wyeth from updating its label, then the failure-to-warn claim would have been preempted. *Id.* at 571–72. But federal law is not that inflexible. Manufacturers do have the power to change their labels, so long as the FDA approves. *Id.*

Because Wyeth never sought to revise its label, the dispositive question for preemption purposes was

whether the FDA would have approved or rejected a stronger IV-push warning had Wyeth sought one. And, on that question, the Court found no "clear evidence that the FDA would not have approved a change to Phenergan's label." *Id.* at 571. Indeed, Wyeth "offered no such evidence." *Id*. at 572. Wyeth did "not argue that it supplied the FDA with an evaluation or analysis" about "the specific dangers posed by the IV-push method." *Id.* at 572–73. The record showed that neither the FDA nor Wyeth "gave more than passing attention to the issue." *Id.* at 572. Nor did Wyeth try to warn about the risks of IV-push, only to be "prohibited from doing so by the FDA." *Id.* To be sure, the FDA had approved Phenergan's label when it first approved the drug for sale. The "mere fact" of approval, however, did not make compliance impossible. Wyeth could have pursued a revision through the CBE process, and failed to show that the FDA would have objected. *Id.* at 573; *see also id.* at 593 (Thomas, J., concurring in the judgment).

Levine thus applied basic preemption principles to drug labeling. While the FDA's *approval* of a label does not itself insulate the manufacturer from tort liability, a manufacturer cannot be held liable for failing to give a warning that the FDA would have disapproved had it been asked.

2. A few years later, this Court in *Mensing* clarified that mere *speculation* about ways in which the manufacturer might have been able to reconcile its federal and state-law duties cannot save a plaintiff's claim from preemption.

In *Mensing*, the plaintiffs alleged that a generic-drug manufacturer failed to warn about a severe

neurological disorder. 564 U.S. at 609. But unlike their brand-name counterparts, manufacturers of generic drugs cannot use the CBE or PAS process. Instead, they "have an ongoing federal duty of 'sameness'"—their labeling "must be the same as the listed drug product's labeling." *Id.* at 613 (quoting 57 Fed. Reg. 17950, 17961 (1992)). As a result, this Court held that it was "impossib[le]" for generic manufacturers to comply with both state and federal law: state law supposedly required a "safer label," but federal law "demanded" a label that matched the brand-name drug's. *Id.* at 618–19.

The plaintiffs argued that the manufacturers could have taken other steps to try to get the brand-name drug's label changed. For instance, they argued (and the Court assumed) that the generic manufacturers had (and breached) a duty to alert the FDA about newly recognized risks. *See id.* at 619. Had that alert been given, it was "certainly possible" that the FDA might have ordered changes to the brand-name label, so that the generic manufacturers "might have eventually been able to strengthen their warning label" too. *Id.* at 620. But because preemption turns on "whether the private party could independently do under federal law what state law requires of it," these "conjectures" did not "suffice to prevent federal and state law from conflicting." *Id.* at 620–21; *see also id.* at 623 (plurality op.) (refusing to consider such "inherent" "contingencies" because "pre-emption analysis should not involve speculation about ways in which federal agency and third-party actions could potentially reconcile federal duties with conflicting state duties").

3. The final case, *Bartlett*, reiterated the two key takeaways from *Levine* and *Mensing*: state law cannot require label revisions that federal law prohibits, and speculative means of dual compliance do not defeat impossibility preemption.

Bartlett involved New Hampshire's design-defect regime, which put a choice to drug manufacturers: either redesign the drugs to make them safer or add a stronger warning. 570 U.S. at 482–84. This Court held that federal law precluded a generic manufacturer from taking either option; it could not alter the drug's composition without thereby creating "a new drug that would require its own NDA," *id.* at 484, and it could not revise its label without running afoul of *Mensing* and the duty of sameness, *see id.* at 486. Because "federal law prohibited ... the remedial action required to avoid liability under New Hampshire law," the claims were preempted. *Id.*

Bartlett also reiterated that plaintiffs cannot avoid preemption by conjuring up speculative scenarios or faux alternatives. The plaintiff in *Bartlett* argued that the manufacturer *could* comply with federal and state law by taking its products off the shelves in New Hampshire. This Court refused to allow that supposed option to defeat preemption. "Our pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability." *Id.* at 488. "Just as the prospect that a regulated actor could avoid liability … by simply leaving the market did not undermine the impossibility analysis in [*Mensing*], so it [was] irrelevant" to the Court's analysis in *Bartlett*. *Id.* at 489–90.

B. Where the FDA Rejects a Request To Add a Warning, Failure-To-Warn Claims Are Preempted.

Levine already established that, even if a manufacturer does *not* seek to revise its label, failure-to-warn claims against it are still preempted if the manufacturer can prove that the FDA would have rejected its attempt. *See* 555 U.S. at 571–72. But *Levine*, *Mensing*, and *Bartlett* also establish a corollary applicable here: if a manufacturer does propose to warn about a risk, discloses the relevant scientific material to the FDA, and is rebuffed, then a later failure-to-warn claim is preempted. A state-law duty to give a warning that the FDA rejected is a duty to violate federal law—and therefore must give way to federal supremacy.

As explained, the FDA has final say over pharmaceutical labeling. *See supra* pp. 3–4. Thus, when the FDA, being fully informed of the available facts, rejects a label revision submitted through the PAS or CBE process, that is the end of the story. The manufacturer may not disregard the FDA's decision and forge ahead on its own. As a matter of law, the state cannot penalize the manufacturer for failure to warn of the health risk that the FDA refused to allow it to warn about. To use *Levine*'s language, the FDA obviously "*would not* have approved a change" to the label, 555 U.S. at 571 (emphasis added), where the FDA in fact *did not* approve a change to the label.

The federal regulatory framework confirms that the FDA's rejection of a request to add a warning is dispositive. After all, the FDA has a statutory duty to respond to new safety information that comes to

its attention: the agency must "promptly notify" the manufacturer of the information; "promptly review" the manufacturer's response; "initiate discussions to reach agreement on whether [or how] the labeling for the drug should be modified to reflect the new safety information"; and, if all else fails, "issue an order directing" the manufacturer "to make such a labeling change as [the FDA] deems appropriate to address the new safety information." 21 U.S.C. § 355(*o*)(4); *see supra* pp. 4–5. The FDA's regulations, too, obligate the agency to work with manufacturers to ensure that any medically appropriate warning makes it onto the drug's label. Thus, if a manufacturer's application contains "easily correctable deficiencies," the FDA will "make every reasonable effort to communicate [them] promptly to applicants" so that they may "correct [them] relatively early in the review process." 21 C.F.R. § 314.102(b). And if the "only deficiencies" in an application "concern editorial or similar minor deficiencies in the draft labeling," the FDA will "approv[e]" the request, "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." *Id.* § 314.105(b).

In short, the FDA has statutory and regulatory duties to oversee drug labeling, respond to new information, and suggest revisions to proposed warnings that are supported by evidence but are (in the FDA's opinion) improperly worded. The FDA's outright *rejection* of a proposed warning by a complete response letter means the agency has concluded that a warning about that risk is not justified. And that turns any state-law failure-to-warn claim into an inappropriate—and preempted—

"second-guess[ing]" of the "FDA's decisionmaking." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 354 (2001) (Stevens, J., concurring in the judgment). That is, since federal law forbids giving a warning that the FDA believes is unjustified, any state-law duty to give such a warning is preempted.

C. Respondents' Failure-To-Warn Claims Are Preempted.

Under this legal framework, respondents' failure-to-warn claims must fail.

Proposed Warning. Merck "proposed to add language to the … Warnings & Precautions … section[] of [Fosamax's] label" to address "atypical femoral fractures." Pet.App.15a. Its cover letter to the FDA noted that the causal relationship between "low-energy subtrochanteric and/or proximal shaft fractures" and bisphosphonate use had not been established. Pet.App.15a. Yet Merck believed it was still "important to include an appropriate statement about them in the product label" to increase physician awareness and help physicians intervene early enough to "possibly prevent[] the progression to complete fracture." Pet.App.15a.

Merck's proposed warning did just that. Titled "Low-Energy Femoral Shaft Fracture," it told physicians that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." Pet.App.15a. Consistent with the reports Merck had received, Merck's proposal also noted that "[s]ome were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma." Pet.App.15a. It then recommended that

doctors evaluate patients with suspected fractures to rule out other possible causes (such as "extreme or increased exercise" or "glucocorticoid use," a known inhibitor of bone remodeling), and to consider "[i]nterruption of bisphosphonate therapy" after evaluating the pros and cons. Pet.App.16a.

FDA Rejection. The FDA rejected Merck's request to add a warning about atypical femoral fractures. The agency's complete response letter recognized that Merck sought to "add[] language to the PRECAUTIONS section and the ADVERSE REACTIONS, Post-Marketing Experience subsection … to describe low-energy fractures at the subtrochanteric region of the femoral shaft." J.A.511 The FDA "agree[d] that atypical and subtrochanteric fractures should be added to the ADVERSE REACTIONS … subsection[ ]" of the labels. J.A.511. But it concluded that Merck's "justification for the proposed PRECAUTIONS section language [was] inadequate." J.A.511. That was a flat, direct rejection, with no hint that the deficiencies were "easily correctable," 21 C.F.R. § 314.102(b), or could be cured by "editorial" changes, *id.* § 314.105(b).

Only after the task force report did the FDA conclude that it was appropriate to warn about the risk of atypical fractures potentially associated with bisphosphonate use. Before that time, the FDA believed that the literature was "conflicting," Pet.App.17a, and that there was no "clear connection" between the fractures and the drug, J.A.519. So the FDA called for "follow[ing] the recommendations in the [unrevised] drug label" while the agency "work[ed] closely with outside experts" to gather "more insight into this issue."

J.A.518–20; *see also* J.A.508 (FDA official's April 2009 email asking Merck to "hold off" on a warning so that FDA could study the issue further and "work with … Merck to decide on language" for a warning "if it is warranted"). Only after an initial report from those "outside experts" did the FDA revisit its approach.

Disclosure of Evidence. Respondents cannot object that Merck hid the ball from the FDA. To the contrary, Merck told the FDA what it knew about the possible link between low-energy femoral fractures and bisphosphonate use. Merck "kept the FDA informed" of "scores of case studies, reports, and articles … documenting possible connections" between the two. Pet.App.13a. A few months before Merck requested the label revisions, it "included over 30 pages of information" on the topic in its periodic safety update, and identified for the agency a host of "recent publications" about it. Pet. App. 14a. Indeed, in June 2008, the FDA stated that it was aware of the issue and had been tracking the safety signals. J.A.666. When the FDA asked for more information on the topic, Merck "promptly complied." There is thus no question—and respondents cannot now dispute, *see* S. Ct. R. 15.2—that Merck fully disclosed the possible connection between its drug and atypical femoral fractures. The FDA rejected its proposed warning with eyes wide open.

* * *

The FDA rejected Merck's request to warn about atypical femoral fractures. Because of that rejection, it was impossible for Merck to revise its label to conform to the state-law duties that respondents allege, without violating federal law in the process.

Respondents' claims—the ones that rest expressly on failure-to-warn theories, along with their disguised failure-to-warn claims that nominally rest on other theories—are therefore preempted.

II. THE THIRD CIRCUIT MISUNDERSTOOD *LEVINE* AND THE REGULATORY SCHEME.

The Third Circuit acknowledged that the FDA rejected Merck's proposed warning, but it held that respondents' claims must go to a jury anyway. According to the Court of Appeals, a jury "could find it less than highly probable" that the FDA would have rejected Merck's proposed warning had it been worded differently. Pet.App.56a–57a. In the Third Circuit's view, Merck must therefore prove to each jury in each individual case—by clear and convincing evidence, no less—that the FDA really meant what it said.

That analysis was wrong, because the Court of Appeals failed to understand the import of the FDA's action on Merck's actual proposal. Unlike in *Levine*, there is no need to resort to counterfactual analysis here; the answer is legally dictated by the course that the agency took in the real world. And, once that much is understood, the Third Circuit's succession of other errors—particularly its heightened standard of proof and its decision to send the question to a jury—become obvious.

A. The FDA's Real-World Action Here Eliminates the Need for Counterfactual Inquiry.

The Third Circuit treated the FDA's rejection of Merck's proposal as simply one piece of evidence for the jury to consider—along with "agency statements,

contemporaneous medical literature, ... and whatever intuitions the factfinder may have about administrative inertia," Pet.App.54a—in evaluating whether the FDA would have approved *any* warning about femoral fractures. The court concluded that a jury, weighing all of those considerations, could find that the FDA rejected Merck's proposal for purely semantic reasons, and thus that the FDA would have approved a differently worded warning about the same health risk. *See* Pet.App.56a, 62a–63a.

That was fundamentally wrong. It is true that, in *Levine*, this Court looked to "an existing fact record to predict the outcome of a hypothetical scenario." Pet.App.45a. But *Levine* considered a counterfactual world because it *had* to. There, "Wyeth … d[id] not argue that it attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA." 555 U.S. at 572. Nor had the FDA given "more than passing attention to the issue." *Id.* Indeed, Wyeth did not even argue "that it supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." *Id.* In such a case—without any agency action on the purported health risk in question—the preemption inquiry turns on whether the FDA "would … have approved a change" had one been sought. *Id.* at 571.

By contrast, where the manufacturer *sought* a change—and a fully informed FDA *rejected* it—there is no reason for any counterfactual inquiry. The FDA's real-world action itself proves—with more than "clear evidence," *id.* at 571—that it would have been impossible to comply simultaneously with state and federal law. *See Dolin v. GlaxoSmithKline LLC*,

__ F. 3d __, 2018 WL 4001208, at *8 (7th Cir. Aug. 22, 2018) (distinguishing *Levine* from cases in which a fully informed FDA rejects a proposed warning after considering the risks).

The Third Circuit resisted that conclusion because it believed there might be space between what happened in the real world and what might have happened in an alternative one. On its view, the FDA might have rejected Merck's proposal because Merck used the supposedly imprecise term "stress fractures." Pet.App.67a. If so, Merck might have been able to change its label after all, in compliance with both state and federal law, if only it had used different terminology. That is, the FDA might have *agreed* with Merck that patients should be warned about atypical femoral fractures, but left the "ball … in Merck's court" to rephrase its warning because "the burden … to correct a drug label rests with the manufacturer, not the FDA." *Id.*

That reasoning—the crux of the Third Circuit's analysis—misunderstands the statutory and regulatory framework. As explained above, the law requires the FDA to work with manufacturers when it believes a label revision is warranted. *See supra* pp. 4–6. To be sure, the manufacturer "bears responsibility for the content of its label at all times"; it cannot do nothing in the face of newly emerging risks. Pet. App. 67a n.162 (quoting *Levine*, 555 U.S. at 570–71); *see also* 21 U.S.C. § 355(*o*)(4)(I). But if the FDA is fully aware of the new data—which, here, Merck provided in its PAS submission—the agency's own duties kick in. Those duties shed light on what an outright rejection by the agency means—that the FDA believes no revision is warranted. And the

FDA's own regulations—unmentioned by the Third Circuit—buttress that conclusion by clarifying that the agency does not reject otherwise-warranted warnings for semantic reasons. *See supra* pp. 5–6.

Any speculation that the FDA rejected Merck's proposal because of its *wording* would thus necessarily rest on the odious notion that the FDA ignored its own legal responsibilities and disregarded the public health. Indeed, the Third Circuit was admirably forthright on this front: it acknowledged that respondents' claims turn on whether the FDA chose to leave patients at risk rather than redline Merck's proposal. Pet.App.61a–62a.

That willingness to second-guess the FDA's conduct and speculate about agency lawlessness conflicts with established law. As a general matter, "a presumption of regularity attaches to the actions of Government agencies." *U.S. Postal Serv. v. Gregory*, 534 U.S. 1, 10 (2001). The Third Circuit was thus not free to impugn the FDA's "proper[] discharge[] of [its] duties" unless "clear evidence" showed that the agency had negligently carried them out. *United States v. Chem. Found.*, 272 U.S. 1, 14–15 (1926). There was no such evidence here: from first to last, the FDA's actions reflected its careful monitoring of the potential relationship between bisphosphonates and atypical femoral fractures. *See supra* pp. 7–16; *infra* pp. 49–50. Moreover, these are precisely the kinds of "conjectures" that *Mensing* (and preemption law more broadly) forbids. 564 U.S. at 621; *see also Buckman*, 531 U.S. at 353 (Stevens, J., concurring) (plaintiffs could not prove that the FDA would have disapproved of certain devices but for the alleged fraud on it, because the FDA "d[id] nothing to

remove the devices from the market, even though it [wa]s aware of the basis for the fraud allegations").

B. The Third Circuit's Approach Also Led It Astray in Other Ways.

In analyzing the hypothetical question of how the FDA would have responded to alternative warnings that Merck could have proposed, the Third Circuit also considered a series of meta-questions about that inquiry: Does it present a question of law or of fact? Should it be answered by a judge or jury? And by what standard of proof must Merck establish that the FDA would have rejected any such warning?

As explained above, the question here is what the FDA *actually did*, not what it *might have* done. And that moots the Third Circuit's analysis of these other questions. Interpretation of the FDA's actual agency action, after all, presents a classic question of law for a judge to decide, and evidentiary burdens of proof are irrelevant. Correcting the Third Circuit's basic legal framework thus also avoids the practical nightmare that, according to the Court of Appeals, necessarily followed: having hundreds of juries independently speculate about the reasons for the FDA's actions based on their own "intuitions" about medical science and administrative practice.

In any event, even if the Third Circuit were right that *Levine* mandates a counterfactual inquiry despite the FDA's real-world action on the purported health risk at issue, the court's answers to these other questions were mistaken. Preemption remains a question of law for a judge to decide, and *Levine* did not adopt a special "clear-and-convincing-evidence" standard for this unexceptional defense.

1. The Third Circuit expended great effort addressing whether its hypothetical question (what the FDA would have done) is a question of fact or law. *See* Pet.App.44a–54a. But the real issue here—the meaning and effect of what FDA *actually* did—is undoubtedly a legal one.

Questions about the meaning of an agency's actions are classic questions of law. For instance, in *B&B Hardware, Inc. v. Hargis Industries, Inc.*, this Court assessed the preclusive effect of a decision by the Trademark Trial and Appeal Board as a pure question of law. 135 S. Ct. 1293, 1302–1310 (2015). It has also assessed the preemptive effect of an agency's action (or inaction) as a question of law. *See, e.g.*, *Hillsborough Cty. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 721 (1985); *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64–68 (2002). Any question about the scope and import of the FDA's decision to reject Merck's PAS must be one of law, too.

Indeed, no one appears to disagree. The Third Circuit acknowledged that "determin[ing] the scope" of an agency's "formal regulatory pronouncement" is a legal task reserved for the court. Pet.App.53a n.135; *see also* Pet.App.52a (courts "determin[e] the … legal effect … of a writing"). It deemed the preemption inquiry to be factual only because it believed that it turned, not on the "legal effect [of the FDA's action] in the first instance," but on the "FDA's likely response to a differently worded proposal," Pet.App.52a—that is, on the counterfactual question rather than the real one.

Respondents were even more emphatic. After oral argument, the Third Circuit *sua sponte* asked for briefing on "the question of whether there is clear

evidence that the FDA would have approved a change to the drug's label is a question of fact or a question of law." Clerk's Letter at 1, No. 14-1900 (3d Cir., June 23, 2016). Respondents argued that, "[t]o the extent the determination depends on construction of final, written regulatory actions by the FDA, that is a [legal] task for the court." Plaintiffs-Appellants' Response Letter at 3, No. 14-1900 (3d Cir., Aug. 25, 2016). Respondents were right in that regard: this case presents a question of law because it turns on the meaning and effect of the FDA's action—namely, its decision to reject Merck's proposed warning. As explained, that agency action preempts respondents' failure-to-warn claims as a matter of law.

For similar reasons, the Third Circuit veered off-course in analyzing whether its hypothetical inquiry is for a judge or a jury. *See* Pet.App.38a–54a. To start, it is unclear why the Third Circuit even reached this question. Reasonable *juries* are entitled to no greater factual leeway than reasonable *judges* at summary judgment. So there was no need to determine the identity of the ultimate factfinder—only whether any genuine dispute of material fact existed.

In any event, the real questions here are purely legal ones about the meaning and effect of the FDA's action. "Bearing, as" they do, "the marks of … 'question[s] of law,'" these questions are "one[s] for the judge," not for hundreds of juries. *Dennis v. United States*, 341 U.S. 494, 515 (1951). There is thus no need to swim through the Third Circuit's counterfactual quagmire, or to endorse a regime under which myriad juries in individual cases all

guess—based on "correspondence, agency statements, contemporaneous medical literature, ... and whatever intuitions the factfinder may have about administrative inertia," Pet.App.23a—about the FDA's position on whether the drug at issue should have carried the warning that plaintiffs claim state law requires.

The Third Circuit's counterfactual approach also led it astray in one final way. In *Levine*, the Court stated that, "absent clear evidence that the FDA would not have approved a change," it would "not conclude" that it was impossible for Wyeth to comply with federal and state law. 555 U.S. at 571. The Third Circuit held that this snippet of the Court's opinion requires drug manufacturers, in order to prevail on a preemption defense, to prove by "clear and convincing evidence" that the FDA would have rejected a proposed warning. Pet.App.37a.

This, too, was an unnecessary distraction. Standards of proof "refer to the degree of certainty by which the *factfinder* must be persuaded of a *factual* conclusion to find in favor of the party bearing the burden of persuasion." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 100 n.4 (2011) (emphases added). These evidentiary standards simply do not apply to "questions of law" like those here. *See id.* at 114 (Breyer, J., concurring); *accord Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Trust for S. Cal.*, 508 U.S. 602, 622 (1993) (explaining that "preponderance of the evidence" and "clear and convincing" are "standard[s] of proof" that direct the "factfinder" on how to "evaluate the raw evidence" in determining "the existence of a fact"). When a court construes a statute or regulation, or interprets the

import of agency action, it does so as a matter of law, and not by applying evidentiary burdens of proof.

2. Even if this really were a case about the hypothetical question of what the FDA would have done under different circumstances, the Court of Appeals erred by treating that as a factual question for a jury, and by reading *Levine* as imposing a heightened standard of proof.

The court appeared to believe that the task in such cases is to psychoanalyze FDA officials and speculate about what they would, in fact, have done. *E.g.*, Pet.App.48a. But that sort of unbounded inquiry would contravene the presumption that officials exercise their responsibilities faithfully in accordance with the law. *See Gregory*, 534 U.S. at 10. The real (hypothetical) question is thus whether the FDA, applying the law in light of the scientific record as it existed at a particular time, would have approved or rejected a proposed warning. That is best understood as a legal question for the court, because it involves interpreting statutes and regulations to determine whether a warning was required given the undisputed historical facts about the scientific data. *See Massachusetts v. EPA,* 549 U.S. 497, 533 (2007) (treating question whether the Clean Air Act required federal regulation of greenhouse gases as a question of law); Pet.App.46a n.122 (noting that "the historical facts are largely undisputed" here). Indeed, even if what the FDA would have done could be seen as a question of fact (or as a mixed question of law and fact), it should belong to a court: the Third Circuit gave no reason that a jury *must* decide this question, and there are many practical reasons for allocating it to a single

judge accustomed to interpreting and applying FDA regulations rather than to myriad juries unfamiliar with those tasks. *See, e.g.*, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388–91 (1996) (judges resolve claim construction in part because of their comparative advantage over jurors "unburdened by training in exegesis" and because of the need for "uniformity").

Last, the Third Circuit's demand for clear and convincing evidence was also incorrect, even if the inquiry were factual or evidentiary. In a "typical civil case involving a monetary dispute between private parties," the plaintiff's burden of proof is "a mere preponderance of the evidence," allowing the litigants to "share the risk of error in roughly equal fashion." *Addington v. Texas*, 441 U.S. 418, 423 (1979); *see, e.g.*, *Penn. State Police v. Suders*, 542 U.S. 129, 137 (2004) (affirmative defenses). This Court has departed from that standard only in rare circumstances, such as when Congress has told it to, *see, e.g.*, *Microsoft*, 564 U.S. at 113–14, or when some unusually compelling interest is involved—say, the importance of parental rights, *Santosky v. Kramer*, 455 U.S. 745, 769–70 (1982), or the dangers of involuntary commitment, *Addington*, 441 U.S. at 433. When lesser (but still weighty) concerns are at stake, the ordinary preponderance standard suffices. *See, e.g.*, *Rivera v. Minnich*, 483 U.S. 574, 579 (1987) (establishing paternity and its resulting obligations); *Steadman v. SEC*, 450 U.S. 91, 102 (1981) (permanently barring someone from investment advising).

Merck's preemption defense falls in the latter camp. To be sure, Plaintiffs allege serious injuries.

But most "monetary dispute[s] between private parties"—and all run-of-the-mill tort suits—involve allegations of serious harm, whether to someone's person, reputation, or business. That alone does not require either party in a slip-and-fall case to prove his position by clear and convincing evidence; such interests are not weighty enough to require one side to shoulder more of the risk of error.

The Third Circuit gave no good reason for its contrary conclusion. Without addressing these background principles, it parsed *Levine*'s single sentence about "clear evidence" as setting forth a "standard of proof," Pet. App. 35a–36a, and then reasoned that "clear evidence" is "synonymous with 'clear and convincing evidence,'" Pet.App.37a.

This result vividly shows why this Court's opinions are "not always to be parsed as though we were dealing with the language of a statute." *Reiter v. Sonotone Corp.*, 442 U.S. 330, 341 (1979). For starters, the Third Circuit was wrong in thinking that the Court has used terms like "clear evidence" consistently to demand heightened proof. Rather, this Court has noted that it has repeatedly used the phrase other than "in the strict evidentiary sense." *Block v. Cmty. Nutrition Inst.*, 467 U.S. 340, 350–51 (1984). *Levine*'s one-off reference to "clear evidence" is best understood to mean that, absent proof of what the FDA actually did or would have done, courts should not lightly assume that the FDA would have rejected a proposed warning. No more, no less.

Indeed, that reading of *Levine*'s reference to "clear evidence" is the only one that makes sense of the rest of the Court's opinion. *Levine* set forth *other*

formulations of the relevant preemption inquiry, like whether the "FDA would have prevented [the manufacturer] from adding a stronger warning." 555 U.S. at 573; *see id.* (whether it "was impossible for [the manufacturer] to comply with both federal and state requirements"). None of these formulations suggests any heightened proof requirement. Why read *Levine*'s lone reference to "clear evidence" to impose one when these other, equally important formulations do not?

The Third Circuit also reasoned that clear and convincing evidence is the proper standard because preemption "is a 'demanding defense' meant to represent a longstanding 'presumption against pre-emption.'" Pet.App.37a (quoting *Levine*, 555 U.S. at 565 n.3, 571–73). But "[i]mpossibility pre-emption is a demanding defense," *Levine*, 555 U.S. at 573, because the defendant must prove that it *could not have* complied with both state and federal law, not just that it would have been hard to do so. Given the inherent difficulty of that defense, there is no reason to tip the scales even more in the plaintiff's favor by skewing the usual burden of proof.

The supposed presumption against preemption is similarly irrelevant. No court has ever suggested that preemption defenses, across the board, must be proven by clear and convincing evidence. *See, e.g.*, *Boyle v. United Techs. Corp.*, 487 U.S. 500 (1988). And a presumption against preemption ignores the Supremacy Clause's *non obstante* provision—its declaration that federal law is supreme, "any Thing in the Constitution or Laws of any State to the Contrary notwithstanding," U.S. Const. art. VI, cl. 2. That language tells courts not to "distort federal law

to accommodate conflicting state law." *Mensing*, 564 U.S. at 623 (plurality op.); *see also* Caleb Nelson, *Preemption*, 86 Va. L. Rev. 225, 256 (2000) (*non obstante* provision "caution[s] against straining the meaning of a federal law to avoid a contradiction with state law"). That is exactly what a general presumption against preemption does. *See* Nelson, 86 Va. L. Rev. at 292–98.

In short, there is no good reason in law or logic to require drug manufacturers to prove what the FDA would have done with evidence as convincing as that needed to strip parents of their children.

* * *

This should have been an easy case. Respondents believe that state law required Merck to warn them about atypical femoral fractures—but Merck tried to do so and the FDA turned it back. There could be no clearer evidence that compliance with both state and federal law was impossible. The Third Circuit's labored contrary conclusion—based on its misreading of *Levine*, its misunderstanding of the FDA's role, and its misapplication of this Court's preemption precedents—must be reversed.

III. IN LIGHT OF THE FDA'S POSITION HERE, MERCK MUST PREVAIL.

Even if Merck were wrong about all of the above, it would still prevail here under the Third Circuit's framework. Merck already offered a host of evidence proving that the FDA would not have allowed Merck to add any warning about atypical femoral fractures. *See supra* pp. 7–16. But in addition to this evidence, Merck now has the very kind of "smoking gun" that the Third Circuit demanded: incontrovertible proof,

from the agency's own mouth, that it would not have authorized respondents' proposed warning until October 2010. Considering this new representation, no reasonable factfinder (judge *or* jury) could conclude that the agency would have permitted a warning about atypical femoral fractures at any earlier time. Merck is therefore entitled to summary judgment even under the Third Circuit's approach. *See* Fed. R. Civ. P. 56. Still, given the importance of these issues in pharmaceutical litigation nationwide, the Court should address the question presented despite the FDA's recent, case-specific comments.

1. The Third Circuit believed that a trial was necessary so that a jury could decide why the FDA rejected Merck's proposed warning—because it believed that no warning was warranted (in which case respondents' claims would be preempted), or because it disliked Merck's terminology (in which case an alternatively worded proposal might have been accepted, reconciling Merck's federal- and state-law duties). *See* Pet.App.62a–63a.

The FDA's certiorari-stage amicus brief now removes any possible doubt about why it rejected Merck's PAS: "FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures *was based on the agency's determination that the data was then insufficient to justify such a warning*." U.S. Cert. Br. 19 (emphasis added); *see also id.* at 22 ("FDA concluded in its Complete Response Letter that the justification for an enhanced warning was insufficient."). "It was only in October 2010—after an external task force had completed its report on the issue—that FDA came to

'believe that the information' about atypical femoral fractures should be added to the Warnings and Precautions section and therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax." U.S. Cert. Br. 22.

The FDA also explained that "[n]o sound basis … exists for concluding that FDA determined in May 2009 that the data was sufficient to warrant a warning but that it rejected [Merck's] proposal because of [Merck's] proposed text." U.S. Cert. Br. 21. The complete response letter "rejected [Merck's] addition because the '*justification* for the proposed [Warnings and Precautions] section language [wa]s inadequate.'" U.S. Cert. Br. 20 (alterations and emphasis in U.S. Cert. Br.). And the FDA's statutory duties and regulatory framework prohibit it from engaging in the callous regulatory behavior that respondents imagine. "If a warning is warranted, FDA will attempt promptly to identify easily correctable deficiencies … with the manufacturer in an iterative process." U.S. Cert. Br. 21. Had the FDA believed a warning were warranted, it would have worked with Merck to develop one, not least because "[s]ection 355(*o*)(4) would have *required*" the FDA to do so. U.S. Cert. Br. 22 (emphasis added); *see supra* pp. 4–5, 19–20.

Even under its erroneous approach, the Third Circuit already thought this was a close case. *See* Pet.App.62a–63a. It is now a slam dunk. Given the FDA's statement, "no reasonable juror could conclude that it is anything less than highly probable that the FDA would have rejected [respondents'] proposed atypical-fracture warning had Merck proposed it … in September 2010." Pet.App.59a.

2. To credit respondents' account of the FDA's actions, this Court would have to ignore both ordinary principles of agency law and the record in this case.

An agency's explanation for its own action is given considerable weight in assessing preemption. In *Geier v. American Honda Motor Co.*, for example, the agency's explanation that it meant to preserve manufacturers' choices when it regulated passive-restraint systems "ma[d]e a difference" in determining whether to allow tort suits forcing manufacturers in a particular direction. 529 U.S. 861, 883 (2000). After all, "Congress ha[d] delegated to [the agency] authority to implement the statute; the subject matter [wa]s technical; and the relevant history and background [we]re complex and extensive." *Id.*; *see also Williamson v. Mazda Motor of Am., Inc.*, 562 U.S. 323, 335–36 (2011) (similarly deferring to the agency's views). Likewise here: if what matters is *why* the FDA rejected Merck's PAS and what the FDA would have done with a revised warning, it makes no sense to disregard the agency's own, direct answers to those questions.

Indeed, it would be particularly inappropriate to disregard the FDA's statements when, as here, the record contains no basis on which a factfinder could do so. The FDA's stated rationale for denying any warning before October 2010 is (at least) consistent with the FDA's complete response letter. *See supra* pp. 34–35. And it also finds conclusive support in the other evidence. The FDA's communications with Merck, its public statements, and its course of conduct all suggest what FDA now asserts: that only *after* the task force's report did FDA "c[ome] to

believe" that bisphosphonate manufacturers ought to warn about atypical femoral fractures. U.S. Cert. Br. 22. There is therefore no reason to disbelieve the FDA's representations to this Court.

Put another way, for this Court to find a genuine dispute as to what the FDA would have done with a rephrased warning, it would have to allow a rational factfinder to conclude either that the FDA misled the Court or that the agency misunderstood its own reasons for its actions. The former contradicts the presumption of regularity. *See supra* p. 39. And *both* options rest on sheer speculation, which is never enough to survive summary judgment, *see Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986), or to avoid preemption, *see Mensing*, 564 U.S. at 621.

Because no rational factfinder could conclude that FDA would have permitted Merck to warn about atypical femoral fractures prior to the task force's report, respondents' state-law failure-to-warn claims are preempted as a matter of law.

3. For these reasons, this Court should reverse the Third Circuit's judgment whether or not it agrees with that court's exposition of the law. In most preemption cases, however, the record will not include express FDA representations removing any ambiguity about the basis for its actions or how it would have responded to counterfactual scenarios. Manufacturers, after all, cannot compel the FDA to say what it would have done with a proposed label. *See United States ex rel. Touhy v. Regan*, 340 U.S. 462, 470 (1951) (agencies have "discretion to submit records voluntarily to the courts"); 21 C.F.R. §§ 20.1, 20.2. Considering the "importance of the pre-

emption issue" more broadly, *Levine*, 555 U.S. at 563, Merck therefore respectfully urges the Court to correct the Third Circuit's legal mistakes, not just reverse its Fosamax-specific judgment.

As Merck explained in its certiorari petition, lower courts applying *Levine* have erected unduly high hurdles to manufacturers' preemption defenses. Pet. 18–25. And a welter of litigation has ensued. *See* Cert. Br. of *Amicus Curiae* Product Liability Advisory Council, Inc., et al., in Support of Petitioner 9–12. Even manufacturers whose conduct is beyond reproach find themselves dragged through years of uncertain litigation. In *Dolin*, for example, the Seventh Circuit had to overturn a jury verdict in the plaintiff's favor even though the FDA had repeatedly rejected efforts to strengthen the drug's warning. __ F.3d __, 2018 WL 4001208; *see also Cerveny v. Aventis, Inc.*, 855 F.3d 1091 (10th Cir. 2017) (litigation even though FDA had "rejected a citizen petition containing arguments virtually identical" to plaintiffs'). Here, Merck faces over a thousand lawsuits even though it fully disclosed what it knew about Fosamax's risks and sought to warn about them.

These examples highlight the recurring nature of the Third Circuit's holdings, and "starkly illustrate[]" the "practical implications" of allowing its erroneous legal framework to stand. U.S. Cert. Br. 23. If manufacturers must face tort suits even when the FDA has made clear that no warning is necessary, they will continue to face an onslaught of troubling, coercive litigation. The Third Circuit's misbegotten legal framework should not stand.

CONCLUSION

The judgment below should be reversed.

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Respectfully submitted,

STEPHANIE PARKER
JONES DAY
1420 Peachtree St., NE
Suite 800
Atlanta, GA 30309

BENJAMIN M. FLOWERS
JONES DAY
325 John H. McConnell Blvd.
Suite 600
Columbus, OH 43215

SHAY DVORETZKY
Counsel of Record
YAAKOV M. ROTH
JEFFREY R. JOHNSON
JONES DAY
51 Louisiana Ave., NW
Washington, DC 20001
(202) 879-3939
sdvoretzky@jonesday.com

Counsel for Petitioner

APPENDIX

APPENDIX A

21 U.S.C. § 355

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. . . .

. . .

. . .

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

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; . . . or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the

conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

. . .

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a

finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. . . .

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

. . .

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

. . .

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

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

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

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

(C) Review

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

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless

the Secretary determines an extension of such discussion period is warranted.

(E) Order

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

(F) Dispute resolution

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

. . .

. . .

. . .

21 CFR § 201.57

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA–approved patient labeling at the end of prescription

drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

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

. . .

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

. . .

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

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

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

. . .

. . .

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

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

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

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

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

. . .

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

term use are different from those for short term use, a statement of the specific indications for each use.

. . .

(3) Dosage and administration.

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

. . .

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

. . .

. . .

. . .

(6) Warnings and precautions.

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

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

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

. . .

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

causal relationship between the drug and the occurrence of the adverse event.

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

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

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in

a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

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

. . .

(9) Use in specific populations. This section must contain the following subsections:

. . .

(v) 8.5 Geriatric use.

. . .

. . .

(d) Format requirements. All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from

which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2–inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

21 CFR § 314.70

(a) Changes to an approved NDA.

(1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an

approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented

in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

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

. . .

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208

of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

. . .

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

. . .

. . .

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

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

. . .

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

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

(b)(3)(vii) of this section must be contained in the supplement.

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

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

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

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

. . .

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

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of

a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

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

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

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

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

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

. . .

21 C.F.R. § 314.71

. . .

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

samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

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

21 C.F.R. § 314.80

(a) Definitions. The following definitions of terms apply to this section:

> Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.
>
> . . .

(b) Review of adverse drug experiences. Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the

scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA adverse drug experience information as described in this section. . . .

. . .

(k) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

. . .

21 C.F.R. § 314.81

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

. . .

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date

of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

> (i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.
>
> . . .
>
> (iii) Labeling.

(a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under § 201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

. . .

(v) Nonclinical laboratory studies. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the

ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) Clinical data.

(a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data

needed to ensure appropriate labeling for the pediatric population shall be included.

. . .

. . .

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

21 C.F.R. § 314.102

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

(b) Notification of easily correctable deficiencies. FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to

facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

. . .

21 C.F.R. § 314.105

. . .

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

. . .

21 C.F.R. § 314.110

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

(1) Description of specific deficiencies. A complete response letter will describe all of the specific

deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

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

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

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

. . .

21 C.F.R. § 314.125

. . .

(b) FDA may refuse to approve an NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

. . .

(6) The proposed labeling is false or misleading in any particular.

. . .

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201.

. . .

. . .

APPENDIX B

RESPONDENTS IN THIS PROCEEDING

Plaintiff	Appeal No.
Albrecht, Doris	14-1900
Molnar, Phyllis	14-2109
Molnar, William	14-2109
Gozdziak, Margaret	14-2110
Duke, Dolores	14-2111
Duke, Thomas	14-2111
Schultz, Susan	14-2112
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Heaton, Nancy	14-2119
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Karch, Lillie	14-2123
Walraed, Susan	14-2124
Sullivan, J. Thomas	14-2124

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Held, Robert T.	14-2235
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Weiss, Robert	14-2236
Hunt, Betty Burch	14-2237
Eisen, Ella	14-2239
Eisen, Herbert	14-2239
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Thomasson, Jack	14-2241
Schendle, Carolyn	14-2242
Schendle, James	14-2242
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