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 RESPONDENTS

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QUESTION PRESENTED

Respondents are more than 500 patients who suffered atypical femoral fractures caused by petitioner's drug, Fosamax. Respondents assert, among other claims, that petitioner failed to warn adequately of atypical femoral fractures. Although federal law permitted petitioner to add warnings to its drug label, petitioner never attempted to add a warning of atypical femoral fractures that would have satisfied its state-law duty. In 2009, the Food and Drug Administration ("FDA") sent a Complete Response Letter to petitioner declining to approve petitioner's proposal to warn of femur fractures that petitioner referred to as "stress fractures." Stress fractures are minor, incomplete fractures that are different from the severe atypical femoral fractures suffered by respondents. FDA explained that petitioner's "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." JA511.

The question presented is:

Whether the Third Circuit accurately assessed the record evidence in concluding that petitioner was not entitled to summary judgment on its preemption defense because petitioner had not shown beyond genuine dispute that FDA would have rejected an adequate warning about atypical femoral fractures.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

CASES

CONSTITUTION, STATUTES, REGULATIONS, AND RULES

LEGISLATIVE MATERIALS

ADMINISTRATIVE MATERIALS

OTHER MATERIALS

In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court held that failure-to-warn claims against brand-name drug manufacturers are not preempted because Congress enacted no applicable express preemption provision, such claims present no obstacle to federal purposes, and compliance with state law is not impossible because federal regulations permit manufacturers to update labeling approved by the Food and Drug Administration ("FDA"). As the Court held in *Levine* and reaffirmed in *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), this rule against preemption gives way only where the manufacturer "show[s], by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate[s] that it would in fact have been impossible to do under federal law what state law required." *Id.* at 624 n.8 (quoting *Levine*, 555 U.S. at 571).

Petitioner Merck Sharp & Dohme Corp. ("Merck") challenges no aspect of that legal framework. This case concerns whether the factual record brings respondents' claims within the narrow, "clear evidence" exception. It does not. Merck's theory rests on mischaracterizations of specific FDA actions. Contrary to Merck's contentions, Merck never proposed the type of adequate warning of atypical femoral fractures sufficient under state law, and FDA never rejected such a warning. Rather, Merck proposed a warning focused on "stress fractures," which are common, minor fractures quite different from the debilitating atypical femoral fractures suffered by Fosamax users. In its Complete Response Letter, FDA rejected the stress-fracture warning because the literature did not support Merck's "[i]dentification of 'stress fractures'" or "[d]iscussion of the risk factors for stress fractures." JA511-12. FDA expressly invited Merck "to resubmit"

a revised warning that "addressed . . . the deficiencies listed." JA512. That FDA action did not preclude Merck from warning adequately of atypical femoral fractures.

Merck's preemption defense thus rests on speculation that FDA would have rescinded a warning that Merck never proposed. Merck bases that speculation on its informal communications with FDA, including its employee's notes purportedly describing her telephone call with an FDA official. The Third Circuit correctly determined that such equivocal evidence cannot support summary judgment. At most, it presents "the possibility of impossibility" that is "not enough" for preemption. *Mensing*, 564 U.S. at 624 n.8.

Merck now denigrates (at 40) as "moot[]" the question the government contended warranted certiorari: whether disputed factual issues regarding preemption should be submitted to judges or juries. Merck is right that the procedural issues addressed by the Third Circuit (the allocation of fact-finding responsibilities and the standard of proof) are irrelevant to whether the Third Circuit's holding reversing summary judgment in Merck's favor should be affirmed. If the Court nonetheless addresses those procedural issues, it should affirm the Third Circuit's handling of those issues and follow the generally applicable rule that the jury decides disputed factual questions.

STATEMENT

A. Statutory And Regulatory Background

1. Since Congress enacted the Federal Food, Drug, and Cosmetic Act ("FDCA") in 1938, FDA has regulated prescription drugs and their labeling. Congress passed the FDCA amidst a background history of state-law tort suits against drug manufacturers, including failure-to-warn claims for dangerous side effects.[1] Congress declined to insert a federal cause of action in the FDCA, determining "that widely available state rights of action provided appropriate relief for injured consumers." *Levine*, 555 U.S. at 574.

Although legislation and FDA regulations have evolved over the past eight decades, two features of the regulatory regime have remained constant. First, "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 570-71.

Second, even as Congress has "enlarged the FDA's powers," it has "t[a]k[en] care to preserve state law." *Id.* at 567. Thus, in 1962, when Congress amended the FDCA to require the manufacturer to prove safety and effectiveness, Congress "added a saving clause, indicating that a provision of state law would only be invalidated upon a 'direct and positive conflict' with the FDCA." *Id.* (quoting Drug Amendments of 1968,

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[1] *See*, *e.g.*, *Halloran v. Parke, Davis & Co.*, 280 N.Y.S. 58, 59 (App. Div. 1935) (per curiam); *Fisher v. Golladay*, 38 Mo. App. 531, 536-43 (1889); *Blood Balm Co. v. Cooper*, 10 S.E. 118, 119 (Ga. 1889); *Thomas v. Winchester*, 6 N.Y. 397, 407-10 (1852); *Fleet v. Hollenkemp*, 52 Ky. (13 B. Mon.) 219, 225-29 (1852).

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793). In addition, "when Congress enacted an express pre-emption provision for medical devices in 1976, it declined to enact such a provision for prescription drugs." *Id.* (citation omitted). To this day, there is no express preemption provision relating to prescription drugs.

2. The FDCA generally forbids the sale of a prescription drug in interstate commerce unless it has been approved by FDA. 21 U.S.C. § 355(a). A manufacturer seeking approval of a brand-name drug must file a new drug application ("NDA") with FDA.[2] An NDA includes proposed labeling. *Id.* § 355(b)(1)(F).

Nothing in the FDCA prohibits a manufacturer from changing the label of a brand-name drug after FDA approval, so long as the label does not render the drug "misbranded." *See id.* §§ 331(a), 352(a) (drug is misbranded "[i]f its labeling is false or misleading in any particular"). Changing an approved label does not, on its own, render a drug misbranded, and this Court has found it "difficult to accept" that "FDA would bring an enforcement action against a manufacturer for strengthening a warning." *Levine*, 555 U.S. at 570.

FDA regulations long have expressly authorized brand-name drug manufacturers to revise labeling unilaterally to strengthen warning language. FDA first promulgated such a regulation in 1965. *See* 30 Fed. Reg. 993, 993-94 (Jan. 30, 1965); 21 C.F.R. § 130.9(d)(1), (e) (1966). Under the current changes being effected ("CBE") regulation, a manufacturer may make "[c]hanges in the labeling to reflect newly acquired information" without prior FDA approval,

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[2] Fosamax is a brand-name drug. Separate statutory and regulatory provisions, not at issue here, govern approval and labeling of generic drugs. *See generally Mensing*, 564 U.S. at 612-17.

if the change is "[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 [21 C.F.R.] § 201.57(c)." 21 C.F.R. § 314.70(c)(6)(iii)(A). "Newly acquired information" includes "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses)." *Id.* § 314.3(b). A manufacturer making such a label change must submit a supplement to FDA regarding the change; if FDA disapproves the CBE supplement, "it may order the manufacturer to cease distribution of the drug product(s) made with the . . . change." *Id.* § 314.70(c)(6)(iii), (c)(7). A manufacturer also can apply for FDA approval to update the label through a "Prior Approval Supplement" ("PAS"), which involves prior approval by FDA. *Id.* § 314.70(b)(2)(v)(A).

3. FDA regulations establish the format of drug labeling. Two sections of the label are relevant here: "Adverse Reactions," and "Warnings and Precautions." The Adverse Reactions section includes a listing of all "undesirable effect[s], reasonably associated with use of a drug." 21 C.F.R. § 201.57(c)(7).[3] A manufacturer must list an adverse reaction if "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse

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[3] Section 201.57 describes labeling requirements for drugs approved on or after June 30, 2001. 21 C.F.R. § 201.56(b)(1). Somewhat different requirements apply to older drugs. *Id.* §§ 201.56(e), 201.80. The three Fosamax drugs implicated in respondents' suits were approved in 1995, 2003, and 2005; the parties and the government agree the labeling requirements for older and newer drugs do not differ in any respect material here, and accordingly address the labeling requirements for newer drugs in § 201.57. *See* U.S. Br. 2 n.1.

event." *Id.* The Warnings and Precautions section describes "clinically significant adverse reactions," "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)." *Id.* § 201.57(c)(6)(i). This section "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." *Id.* Since 2008, those standards also have applied to warnings added through a CBE supplement. *Id.* § 314.70(c)(6)(iii)(A).

If FDA "determines that [it] will not approve" either an NDA or a labeling supplement "in its present form," it will "send the applicant a complete response letter." *Id.* § 314.110(a). The complete response letter "will describe all of the specific deficiencies that the agency has identified in an application." *Id.* § 314.110(a)(1). The purpose of a complete response letter is "to inform[] sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application." 73 Fed. Reg. 39,588, 39,589 (July 10, 2008). FDA provides three options to an applicant who has received a complete response letter: (1) "[r]esubmit the application . . . , addressing all deficiencies identified in the complete response letter"; (2) "[w]ithdraw the application"; or (3) request a hearing at which FDA will make a final determination whether to approve or reject the application. 21 C.F.R. § 314.110(b).

4. Until the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), FDA lacked authority to mandate that manufacturers change prescription drug labels. *See Levine*, 555 U.S. at 571.

The FDAAA gave FDA authority to initiate a process to mandate label changes if FDA "becomes aware of new safety information" that FDA "believes should be included in the labeling of the drug." 21 U.S.C. § 355(*o*)(4)(A). Congress included a "[r]ule of construction" that "[t]his paragraph shall not be construed to affect the responsibility of the [manufacturer] to maintain its label in accordance with existing requirements, including . . . [21 C.F.R. §] 314.70." *Id.* § 355(*o*)(4)(I).

B. Factual History

1. Respondents are more than 500 individuals (or their spouses or representatives) from roughly 45 States who allege that they suffered an atypical femoral fracture ("AFF") caused by their use of Fosamax, a brand-name osteoporosis drug manufactured by petitioner. Pet.App.75a-95a; Resp. C.A. Br. Jurisdictional App. Respondents suffered their injuries between January 1999 and September 2010. MDL Dkt. 2857-2.

An atypical femoral fracture is a debilitating fracture in which the thigh bone, or femur, often breaks in two. JA288-89; *see also* JA290, 336, 388, 410, 662 (x-rays). Atypical femoral fractures generally occur in the proximal (or upper) third of the femoral shaft, and may occur in the subtrochanteric region, which is just below the two protuberances (called trochanters) at the top of the femur. JA288-92. Atypical femoral fractures are low-energy fractures, meaning they are associated with no trauma or minimal trauma. JA292. They generally have a transverse or short oblique configuration, meaning the fracture cuts across the bone, perpendicular to the femoral shaft (or slightly slanted). *Id.*

2. FDA approved Fosamax in 1995 to treat osteoporosis and in 1997 to prevent osteoporosis; post-menopausal women most commonly use the drug. Pet.App.5a, 12a-13a. Fosamax's scientific name is "alendronate sodium" (sometimes shortened to "alendronate"), and Fosamax belongs to a class of drugs called bisphosphonates that are commonly used to treat osteoporosis. JA192 (Fosamax Jan. 2011 label).[4]

Human bones constantly undergo a rebuilding process called remodeling or turnover. JA102 (Burr Decl. ¶ 13). In the remodeling process, bone breaks down (resorption) and new bone cells form at that same location (formation). *Id.* Bone remodeling repairs and removes microcracks, which are small fractures that accumulate through normal activity. *Id.* In post-menopausal women, the rate of resorption often exceeds that of formation, leading to bone loss. *Id.*

Fosamax reduces bone resorption by inhibiting the activity of bone-resorbing cells called osteoclasts. JA197 (Fosamax Jan. 2011 label). Fosamax "ultimately reduce[s]" bone formation because it inhibits bone resorption, and "bone resorption and formation are coupled during bone turnover." JA198. According to the expert report of Dr. David Burr, one of the world's leading orthopedic scientists, the "significant reduction in bone turnover" can "increase bone mass, but numerous studies demonstrate that it also creates older bone and negatively affects bone tissue quality."

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[4] In 2003 and 2005, respectively, FDA approved variants of Fosamax in an oral solution and in a tablet combined with Vitamin D called "Fosamax Plus D." *See* U.S. Br. 2 n.1. No party contends the relevant labeling history or preemption analysis differs with any of the three Fosamax variants. This brief uses "Fosamax" to refer collectively to all three Fosamax products.

JA102-03 (Burr Decl. ¶¶ 14-15). Long-term bisphosphonate use "affect[s] the material properties of bone over time by reducing bone toughness and its ability to repair microcracks." JA144 (*id.* ¶ 84). Consequently, long-term Fosamax users may suffer incomplete fractures that "continue to grow until complete fracture of the bone." JA144-45 (*id.* ¶ 84); Pet.App.6a.

The type of femoral fractures associated with Fosamax use are called atypical femoral fractures, or AFFs. JA101 (Burr Decl. ¶ 12). Because of the surge in these previously rare fractures among Fosamax patients, by 2002, leading orthopedic surgeons dubbed them "Fosamax Fracture[s]." JA126 (*id.* ¶ 52); JA448; C.A.App.1254.

3. Evidence connecting Fosamax and other bisphosphonates to atypical femoral fractures emerged over time. In internal discussions in 1990 and 1991, when Fosamax was undergoing early clinical trials, Merck scientists expressed concern that Fosamax could inhibit bone remodeling to such a degree that "inadequate repair may take place" and "micro-fractures would not heal." JA111-13 (Burr Decl. ¶¶ 25-28); C.A.App.1180, 2462-63. A 1995 Merck report on a Fosamax clinical trial demonstrated significant reduction in bone turnover. C.A.App.2548-50.

In 1999, Merck began receiving adverse event reports indicating long-term Fosamax users were suffering atypical femoral fractures. JA122-25 (Burr Decl. ¶¶ 45-50) (describing reports). In 2005, Merck received a report from orthopedic surgeon Dr. Joseph Lane of "25 patients with long bone fractures that . . . have taken Fosamax . . . for a long time," noting that in his hospital they call such a fracture the "Fosamax

Fracture." JA126 (*id.* ¶ 52) (last alteration in original); *see* JA448. Other orthopedic physicians similarly raised concerns about fractures resulting from long-term Fosamax use. JA462-63, 649-51. Also in 2005, Merck performed a statistical data-mining analysis of Fosamax adverse event reports, concluding that these reports revealed a statistically significant incidence of femur fractures beginning in September 2003. C.A.App.1272-73, 1443. Respondents' biostatistician expert David Madigan confirmed that FDA's adverse event database for Fosamax showed a statistically significant signal in 2005 of a relationship between Fosamax and femur fractures. JA189-91. In 2006, a Merck regulatory-affairs employee in Singapore reported learning of eight cases of atypical femoral fractures suffered by long-term Fosamax users and suggested that they "might be a signal for a label update." JA452, 455-56.

Scholarly articles and case studies documented the connection between bisphosphonates and atypical femoral fractures. A 2004 article studied several Fosamax patients who had suffered atypical femoral fractures and concluded "[o]ur findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures." JA416. A 2008 article studied 25 Fosamax users who had suffered atypical femoral fractures, concluding that such fractures were "associated with alendronate use." JA386.[5] As the Third Circuit summarized, "[b]etween 1995 and 2010, scores of case studies, reports, and articles were

[5] *See generally* JA106-10, 116-22 (Burr Decl. ¶¶ 19-24, 35-44) (describing numerous studies connecting Fosamax or bisphosphonates generally to weakened bone or atypical femoral fractures).

published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." Pet.App.13a.

Fosamax not only carries significant risks, but also has not been shown to reduce fractures for many users, including patients without osteoporosis or a preexisting vertebral fracture. JA179 (Furberg Decl. ¶ 64). Fosamax is commonly prescribed to patients who have below-average bone density but not osteoporosis. In one of Merck's clinical trials of Fosamax use by such patients, the Fosamax-treatment group suffered more fractures than the placebo group. JA167 (*id.* ¶ 40). Merck's Director of Clinical Research acknowledged in sworn testimony that "[t]here's no evidence" Fosamax "reduces the risk of fracture in women who don't have osteoporosis." JA460 (Santora Dep. 796). Even among patients with osteoporosis, there is no demonstrated fracture-reduction benefit beyond three years of use. JA179 (Furberg Decl. ¶ 66).

4. Fosamax's label contained no mention of femur fractures from its approval in 1995 through 2008. Pet.App.12a-14a. In June 2008, FDA informed petitioner that it was "aware of reports" of bisphosphonate users suffering atypical femoral fractures and was "concerned about this developing safety signal." JA280.

In September 2008, petitioner submitted a PAS application to FDA to add mentions of fractures to both the Adverse Reactions and the Warnings and Precautions sections of the Fosamax label. JA669. Merck proposed adding a reference to "low-energy femoral shaft fracture" in the Adverse Reactions section and to cross-reference a longer discussion in the Warnings and Precautions section. JA728. In the

Warnings and Precautions section, Merck proposed to add the following language:

> *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 bisphosphonate. ***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.

JA707 (emphases added).

Every sentence after the first sentence referred to the femur fractures as "stress fractures." A stress fracture is different from an atypical femoral fracture. A stress fracture is "an incomplete fracture of a long bone," the vast majority of which "never progress to a full and complete fracture," and which is generally treated "by prescribing rest or inactivity in the

affected bone." JA144 (Burr Decl. ¶ 83). By contrast, atypical femoral fractures often progress to a "completed subtrochanteric fracture" of the femur and are "much more significant than 'garden-variety' stress fractures, which usually heal uneventfully with simple rest and without full fracture." JA145-46 (*id.* ¶ 86). As FDA explained in 2010, characterizing atypical femoral fractures as "stress fractures" would "contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use" because, "for most practitioners, the term 'stress fracture' represents a minor fracture." JA566. Merck also acknowledged that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." C.A.App.1573.

Figure 1 is an x-ray of an atypical femoral fracture suffered by an alendronate user; Figure 2 is an x-ray of a stress fracture of the femoral shaft.

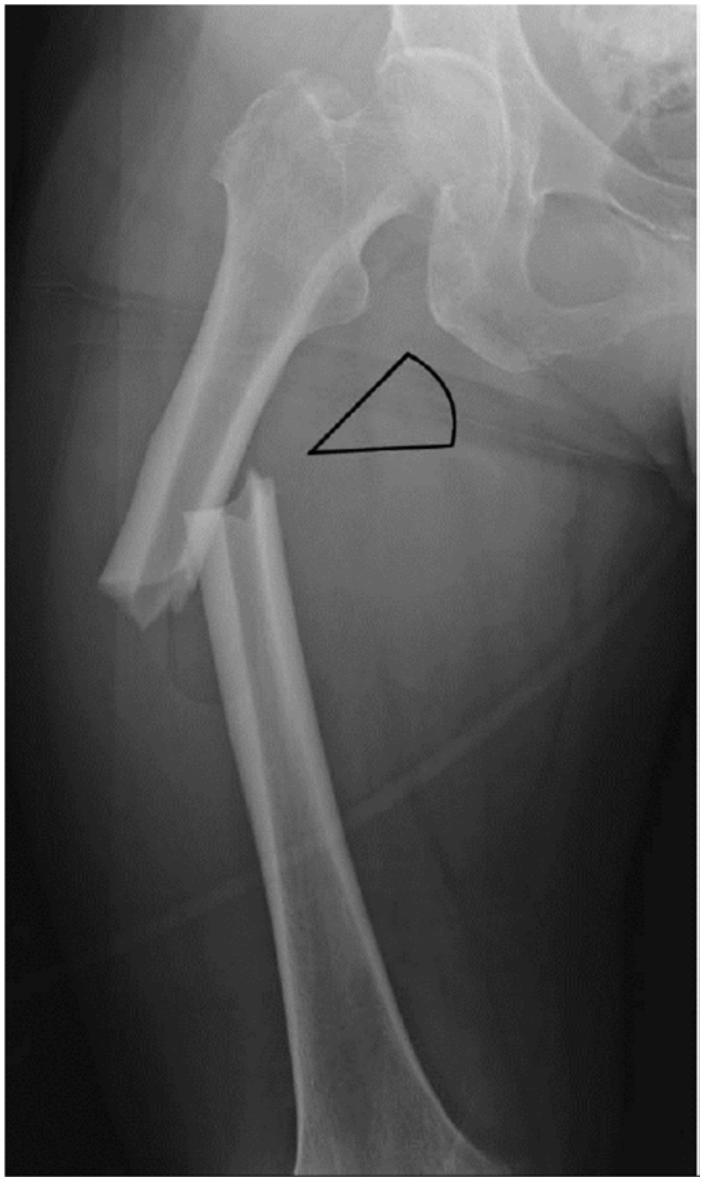

Figure 1: atypical femoral fracture suffered by Fosamax user[6]

[6] JA388.

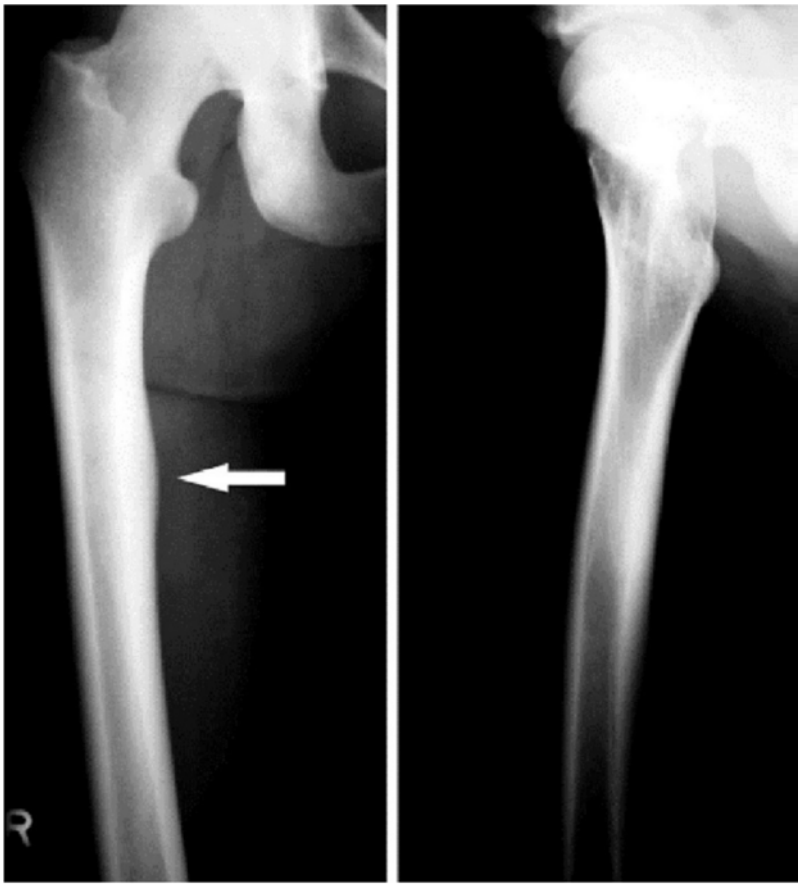

Figure 2: stress fracture of the femoral shaft[7]

On May 22, 2009, FDA sent Merck a "Complete Response" letter by Dr. Scott Monroe, granting in part and denying in part petitioner's application. JA510-13. FDA approved the addition of "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section, JA512, reflecting the conclusion "there is some basis to believe" Fosamax causes those

[7] Alan Ivkovic et al., *Stress fractures of the femoral shaft in athletes: a new treatment algorithm*, 40 Br. J. Sports. Med. 518 (2006), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2465093/.

fractures, 21 C.F.R. § 201.57(c)(7). Regarding the proposed Warnings and Precautions language, FDA responded:

> [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.

JA511-12. FDA invited Merck to "resubmit" its application and to "fully address all the deficiencies listed." JA512.

In June 2009, Merck withdrew its PAS application and added the approved femur-fracture language to the Adverse Reactions section of the Fosamax label through a CBE supplement, but did not add any reference to femur fractures in the Warnings and Precautions section. JA274, 279, 657. Merck has submitted no evidence it took any action to resubmit its application or worked with FDA on atypical-femoral-fracture language for the Warnings and Precautions section at that time.

5. On March 10, 2010, FDA issued a drug-safety communication that it was "working closely with outside experts," including a Task Force of the American Society for Bone and Mineral Research ("ASBMR Task Force"), "to gather additional information that may provide more insight" into the connection between bisphosphonates and atypical femoral fractures. JA519-20.

On September 14, 2010, the ASBMR Task Force published a report describing the features of atypical

femoral fractures, JA288-93, and concluding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture," JA355. According to Dr. Burr, a principal author of the report, the Task Force did not conduct any additional clinical research; it simply "review[ed]" "the currently available information," most of which was available before May 2009. JA133-34 (¶ 62).

On October 13, 2010, FDA announced it would require all bisphosphonate manufacturers to warn of atypical femoral fractures. JA246. That same day, FDA proposed specific language for the Fosamax label, describing "[a]typical femoral fractures" in the Warnings and Precautions section. JA528-29. FDA explained that, although "it is not clear if bisphosphonates are the cause, . . . these atypical fractures may be related to long-term bisphosphonate use." JA247. Merck proposed revised language that added five references to "stress fractures," including the language relating to risk factors for stress fractures that FDA had rejected in 2009. JA606-07. FDA sent Merck a redline substantially rewriting Merck's proposal; FDA struck out each reference to stress fractures and revised the language so that it was nearly identical to what FDA originally proposed. *Id.*; *compare* JA528-29 (initial FDA proposal). FDA explained that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." JA566.

In January 2011, Merck added a three-paragraph discussion of atypical femoral fractures to the

Warnings and Precautions section of the Fosamax label, which remains on the label today. JA223-24. With the heading "*Atypical Subtrochanteric and Diaphyseal Femoral Fractures*," the language states that "[a]typical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients." JA223. It describes atypical femoral fractures as being "transverse or short oblique in orientation" and advises that patients with symptoms of an atypical femoral fracture should consider "[i]nterruption of bisphosphonate therapy." JA223-24. The warning now refers to the fractures five times as "atypical" without using the term "stress fracture." *Id.*

C. Procedural History

1. In May 2011, the Judicial Panel on Multidistrict Litigation ordered 36 then-pending actions involving claims that Fosamax or its generic equivalents caused femur fractures to be centralized for consolidated pretrial proceedings in the District of New Jersey in a multi-district litigation ("MDL"). *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F. Supp. 2d 1355 (J.P.M.L. 2011). Respondents' actions were filed in or transferred to the Fosamax MDL. Pet.App.75a-95a.

Although the complaints differ in their particularities, respondents generally alleged that Fosamax caused them to suffer atypical femoral fractures and that Merck is liable for respondents' injuries because, among other reasons, Merck failed to warn about atypical femoral fractures in a way that would apprise respondents or their physicians of the risks. For example, Lorice Cortez alleged that she took Fosamax from 1999 through 2010 and, "[a]s a result of using . . . Fosamax," she "suffered from a fracture of her left

femur" on August 31, 2009, at age 70. Cortez Compl.[8] ¶¶ 50-51, 54. "[W]hile turning to unlock the front door of her house, Mrs. Cortez[] heard a popping sound then she suddenly felt her left leg give out from beneath her." Braniff Decl.[9] ¶ 144. Her fracture required surgery, in which her leg was repaired by a rod and screws. Cortez Compl. ¶ 55. She alleged Merck "failed to change" its labeling "to warn of the potential for femur fractures" and "did not provide adequate warnings . . . about the increased risk of serious adverse events." *Id.* ¶¶ 39, 46. She explained she "would not have used Fosamax for so many years had Defendant properly disclosed the risks associated with its long-term use." *Id.* ¶ 58.[10]

2. In April 2013, the district court held the first bellwether trial in a case brought by Bernadette Glynn and her husband (who are not respondents here). Pet.App.24a-25a; C.A.App.2093-94. No respondent was a party to the *Glynn* action. Merck had filed motions for summary judgment and judgment as a matter of law on preemption, but the court reserved judgment on those motions and submitted the Glynns' failure-to-warn claim to the jury. Pet.App.163a-164a. On April 29, 2013, the jury found against the Glynns, deciding in a special verdict that Ms. Glynn failed to prove "she experienced an atypical femur fracture in April 2009." JA45.

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[8] Compl., *Cortez v. Merck Sharp & Dohme Corp.*, No. 3:11-cv-05025-FLW-LHG, Dkt. #1 (D.N.J. Aug. 31, 2011).

[9] MDL Dkt. 2946, Ex. A.

[10] *See also*, *e.g.*, JA40-42 (Knopick Compl. ¶¶ 41, 43, 57, 59); JA26-27, 29, 32-33 (Steves Compl. ¶¶ 62, 73, 83, 123, 125); JA639-40, 642 (Jones Compl. ¶¶ 61, 64, 66, 73).

On June 27, 2013, after the jury's defense verdict, the district court issued an unusual advisory opinion, concluding that federal law preempted the Glynns' claims. Pet.App.153a-174a. The court reasoned that FDA's rejection of Merck's proposed "stress fracture" warning language in the Warnings and Precautions section in 2009 provided "'clear evidence'" that Merck could not have added any warning of atypical femoral fractures to the Fosamax label. Pet.App.168a-174a (quoting *Levine*, 555 U.S. at 571).

On August 1, 2013, five weeks after the preemption advisory opinion in *Glynn*, Merck moved for the district court to issue an order to show cause why all cases in the MDL alleging injuries before September 14, 2010, should not be dismissed as preempted. MDL Dkt. 2857-1. Respondents objected to this procedure. JA50-56. The court entered the order to show cause as Merck proposed, giving respondents 45 days to respond. JA86-88.

Respondents opposed preemption. Respondents also argued that it would be procedurally improper to dismiss their claims on preemption grounds through the show-cause procedure. MDL Dkt. 2995-3.

The district court granted summary judgment to Merck and held that respondents' claims were preempted. Pet.App.113a-152a. The court concluded that, because of the *Glynn* advisory opinion, "the burden is therefore shifted to [respondents]" to defeat summary judgment. Pet.App.132a. It held that failure-to-warn claims based on the Warnings and Precautions section were preempted because the court had "already considered and rejected" respondents' arguments in *Glynn*. Pet.App.150a. The court rejected failure-to-warn claims based on the theory that Merck should have added a warning earlier to the

Adverse Reactions section, asserting that the theory was not adequately pleaded. Pet.App.147a-148a. The court also held that respondents' non-failure-to-warn claims were preempted because the court concluded — on the basis of a single allegation in a single complaint — that all of respondents' non-failure-to-warn claims were "merely disguised failure to warn causes of action." Pet.App.142a.

3. The Third Circuit vacated the district court's grant of summary judgment to Merck. Pet.App.4a. The court framed the question as whether the evidence that "FDA would have approved a properly-worded warning about the risk of thigh fractures" was sufficient for respondents to survive summary judgment. Pet.App.5a.

The Third Circuit concluded Merck was not entitled to summary judgment. The court held the record reasonably supported respondents' view that FDA rejected Merck's proposed warning "based on Merck's misleading use of the term 'stress fractures' rather than any fundamental disagreement with the underlying science" and that "FDA would not have rejected [a] proposed warning" of atypical femoral fractures. Pet.App.63a. The Third Circuit noted that "Merck repeatedly characterized the fractures at issue as 'stress fractures,'" Pet.App.65a, and that "[s]tress fractures are usually incomplete fractures that heal with rest, while atypical femoral fractures often are complete fractures that require surgical intervention," Pet.App.66a.

The Third Circuit read the Complete Response Letter as supporting respondents' position. That Letter criticized Merck's proposed "'[i]dentification of "stress fractures"'" and "'[d]iscussion of the risk factors for stress fractures,'" and "FDA did not give

any other reason for rejecting Merck's proposed warning." *Id.* (quoting JA511). The court reasoned that "[t]he combination of § 314.110's 'complete description' requirement" of all deficiencies in a complete response letter and "FDA's silence" in the Complete Response Letter concerning any lack of scientific evidence that Fosamax causes atypical femoral fractures "could certainly permit an inference about the FDA's contemporaneous thinking, and thereby an additional inference about how the FDA would have responded to a different warning." Pet.App.53a n.135.

The Third Circuit decided that, on remand, a jury, rather than a judge, should resolve the disputed factual questions presented by Merck's preemption defense. Pet.App.54a. The Third Circuit acknowledged "that courts are typically charged with determining the construction (*i.e.*, the legal effect) of a writing," such as the Complete Response Letter. Pet.App.52a. But that Letter did not resolve "whether the FDA would have approved a different label amendment than the one it actually rejected in the May 2009 letter." *Id.*

The court reasoned that, in this case, whether FDA would have rejected an adequate warning of atypical femoral fractures was a factual question within the traditional competence of juries because "an assessment of the probability of a future event should generally be categorized as a finding of fact," Pet.App.45a, which requires "weigh[ing] conflicting evidence and draw[ing] inferences from the facts — tasks that the Supreme Court tells us 'are jury functions, not those of a judge,'" Pet.App.47a (quoting *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986)). Merck stated at oral argument that its "single

best piece of evidence" in support of preemption was a memorandum written by Merck employee Charlotte Merritt ("Merritt memorandum") of a telephone call she had with Dr. Monroe of FDA in which he purportedly discussed the "conflicting nature of the literature" on atypical femoral fractures. Pet.App.49a n.125. Merck's reliance on the call notes confirmed for the Third Circuit the presence of disputed factual issues suitable for resolution by the jury: "at a minimum," a decisionmaker would need to make credibility determinations about Merck's employee, interpret the meaning and accuracy of the notes, infer the FDA official's intent, and then weigh those factors. *Id.*

The Third Circuit also interpreted *Levine* as imposing a "clear and convincing evidence" standard for a brand-name drug manufacturer's preemption defense, requiring the manufacturer to show that it was "highly probable that the FDA would not have approved a change to the drug's label." Pet.App.37a.[11]

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[11] The Third Circuit also held that Merck is not entitled to summary judgment on respondents' failure-to-warn claims involving the Adverse Reactions section of the Fosamax label or on respondents' non-failure-to-warn claims. Pet.App.69a-74a. Merck did not challenge those rulings in its certiorari petition and thus has forfeited any argument regarding the Third Circuit's decision to remand those claims. *See* Cert. Opp. 1; Sup. Ct. R. 14.1(a). Merck's half-sentence attempt (at 36) to revive a challenge to the non-failure-to-warn claims in its merits brief is improper and insufficient to properly present the issue in any event. *See*, *e.g.*, *Anza v. Ideal Steel Supply Corp.*, 547 U.S. 451, 461 (2006) ("declin[ing] to address" argument that "has not been developed").

SUMMARY OF ARGUMENT

I.A. Failure-to-warn claims against brand-name drug manufacturers are not preempted absent clear evidence that FDA would have rescinded an adequate warning. The FDCA contains no applicable express preemption clause. Nor do failure-to-warn claims obstruct federal purposes. *See Levine*, 555 U.S. at 574.

B. Nothing in federal law makes it impossible for brand-name drug manufacturers to comply with a state-law duty inherent in a failure-to-warn claim by adding adequate warnings to an FDA-approved label. No provision of the FDCA prohibits such changes, and the CBE regulation expressly permits unilateral label changes to strengthen warnings. *See Levine*, 555 U.S. at 568; 21 C.F.R. § 314.70(c)(6)(iii)(A). Therefore, to establish impossibility preemption, the manufacturer must "show, by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required." *Mensing*, 564 U.S. at 624 n.8 (quoting *Levine*, 555 U.S. at 571.

C. As *Levine* recognized, the FDAAA did not change the preemption analysis. When Congress authorized FDA to mandate label changes, it preserved manufacturers' ability to add such changes unilaterally and enacted a "[r]ule of construction" that FDA's new authority "shall not be construed to affect the responsibility of" the manufacturer "to maintain its label in accordance with existing requirements," including the CBE regulation. 21 U.S.C. § 355(*o*)(4)(I); *see Levine*, 555 U.S. at 571. FDA still relies on manufacturers to make most label changes. Thus, where FDA has not yet mandated a label change, one cannot infer that FDA would have rescinded a manufacturer's CBE supplement.

II. Merck failed to show, by clear evidence, that FDA would have rescinded an adequate warning of atypical femoral fractures.

A. The Complete Response Letter does not carry Merck's burden. Merck proposed to warn of minor "stress fractures," and its application did not accurately describe the atypical femoral fractures suffered by respondents. As the Complete Response Letter explained, FDA rejected Merck's proposal because of the inaccurate stress-fracture language. FDA also invited Merck to submit a revised warning that fixed this problem. JA511-12. That is consistent with the general function of complete response letters, which reject applications "in [their] present form," 73 Fed. Reg. at 39,589, while informing applicants of all deficiencies that must be remedied to obtain approval, *see* 21 C.F.R. § 314.110(a)(1). Merck's and the government's reading of the Complete Response Letter — as a final rejection of an atypical-femoral-fracture warning — cannot be squared with its text or the regulatory context. All the Complete Response Letter rejected was Merck's stress-fracture warning.

B. The informal FDA communications on which Merck relies also fail to prove impossibility. The Merritt memorandum, which Merck presented below as its "single best piece of evidence," Pet.App.49a n.125, raises factual questions regarding the accuracy of Merritt's notes and the meaning of the FDA official's reported remarks. FDA's earlier email stating it wanted to "work with" Merck on alternative warning language supports respondents because it contradicts Merck's position that FDA definitively rejected any label change. JA508.

C. FDA's actions in mandating an atypical-femoral-fracture warning in 2010 confirm that Merck

could have added a warning earlier. FDA was swayed to mandate the warning by the ASBMR Task Force report, which merely "summarized" existing "data," JA249, and "helped [FDA] understand these fractures a little bit better," JA494, by "clarify[ing] the features of atypical femur fractures," JA488. FDA presumably would have welcomed a similarly clarifying supplement from Merck, rather than its confusing stress-fracture label application.

III.A. Disputed factual questions regarding pre-emption should be presented to the jury. In civil actions at law, judges handle legal questions, while "predominantly factual issues are in most cases allocated to the jury." *City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 720 (1999). "[W]hether the facts establish the conditions for" a preemption defense "is a question for the jury." *Boyle v. United Techs. Corp.*, 487 U.S. 500, 514 (1988). Respondents agree with Merck and the government that the legal effect of the Complete Response Letter is a judge question. But that legal effect was limited to rejecting Merck's stress-fracture warning. Whether FDA would have rescinded a different warning presents the type of counterfactual question juries routinely decide.

B. The Third Circuit correctly applied a height-ened standard of proof of impossibility. The FDCA and the CBE regulation make compliance with state law possible; to assert an impossibility-preemption defense based on speculation that FDA will take some future action to halt compliance with state law requires a persuasive showing. Nonetheless, it makes no difference to the outcome here whether this Court views "clear evidence" as imposing a "clear and convincing evidence" standard of proof or, as

the government contends (at 26), an "*interpretive* presumption against preemption."

C. In all events, the district court's judgment cannot stand because the court dismissed respondents' claims through a cursory show-cause procedure following an advisory opinion issued in another action to which respondents were not parties. Although the Third Circuit's disposition made it unnecessary to reach respondents' objections to the show-cause procedure, the district court's judgment could not be upheld without addressing those objections.

ARGUMENT

I. FAILURE-TO-WARN CLAIMS AGAINST BRAND-NAME DRUG MANUFACTURERS ARE NOT PREEMPTED UNLESS THE MANUFACTURER SHOWS BY CLEAR EVIDENCE THAT FDA WOULD HAVE RESCINDED AN ADEQUATE LABEL CHANGE

Federal law generally does not preempt failure-to-warn claims against brand-name drug manufacturers. No statute or regulation expressly preempts such claims, and failure-to-warn claims do not conflict with any aspect of the federal regulatory scheme. FDA regulations expressly permit (and in fact require) brand-name drug manufacturers to add warnings to FDA-approved labels to keep pace with scientific evidence of the drug's risks and to comply with state law.

A. The FDCA Does Not Expressly Preempt Failure-To-Warn Claims Against Brand-Name Drug Manufacturers, And Such Claims Pose No Obstacle To The Statute's Purposes

"Pre-emption of state law . . . occurs through the 'direct operation of the Supremacy Clause.'" *Kurns*

v. Railroad Friction Prods. Corp., 565 U.S. 625, 630 (2012) (quoting *Brown v. Hotel & Rest. Emps.*, 468 U.S. 491, 501 (1984)). "'[T]he purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Levine*, 555 U.S. at 565 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)).

1. When Congress enacts a statute within its constitutional authority containing an express pre-emption clause, state law is preempted to the extent covered by that provision. *See*, *e.g.*, *Gobeille v. Liberty Mut. Ins. Co.*, 136 S. Ct. 936, 943 (2016). Congress never has enacted an express preemption provision applicable to prescription drugs in the FDCA's 80-year history. Although Congress enacted a preemption provision for medical devices in 1976, it did not do the same for prescription drugs. *See Levine*, 555 U.S. at 574.

2. Failure-to-warn claims against brand-name drug manufacturers pose no "obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). This Court so held in *Levine*. There, FDA had appended a preamble to a drug-labeling regulation, which "declared that the FDCA establishes 'both a "floor" and a "ceiling,"' so that 'FDA approval of labeling . . . preempts conflicting or contrary State law.'" 555 U.S. at 575 (quoting 71 Fed. Reg. 3922, 3934-35 (Jan. 24, 2006)) (alteration in original). The Court rejected the preamble and Wyeth's reliance on it, concluding that "all evidence of Congress' purposes [wa]s . . . contrary" to the floor-and-ceiling argument. *Id.* at 574. The fact that Congress, while aware of prevalent state drug litigation, neither enacted a preemption clause nor a federal right of action was "powerful evidence that Congress did not intend FDA

oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 575.[12]

B. A Brand-Name Drug Manufacturer Has The Power To Strengthen A Drug Label To Comply With State Law

State law is preempted "where it is 'impossible for a private party to comply with both state and federal requirements.'" *Mensing*, 564 U.S. at 618 (quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995)). "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Id.* at 620.[13]

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[12] Justice Thomas concluded he could "no longer assent" to purposes-and-objectives preemption because it "giv[es] improperly broad pre-emptive effect to judicially manufactured policies, rather than to the statutory text enacted by Congress pursuant to the Constitution and the agency actions authorized thereby." *Levine*, 555 U.S. at 604 (Thomas, J., concurring in the judgment). In any event, purposes-and-objectives preemption does not apply to failure-to-warn claims against brand-name drug manufacturers because Congress consistently has preserved state law and manufacturers' authority to update their labels. *See id.* at 566-68 (majority).

This Court also has found preemption where federal law occupies an entire field. *See*, *e.g.*, *Hughes v. Talen Energy Mktg., LLC*, 136 S. Ct. 1288, 1297 (2016). Merck never has argued for field preemption here, nor could it. *See Levine*, 555 U.S. at 567 (Congress has "t[a]k[en] care to preserve state law").

[13] A preemptive "direct conflict" also may occur "if federal law gives an individual the right to engage in certain behavior that state law prohibits." *Levine*, 555 U.S. at 590 (Thomas, J., concurring in the judgment). Such a conflict does not exist here because federal law "do[es] not give drug manufacturers an unconditional right to market their federally approved drug at all times with the precise label initially approved by the FDA." *Id.* at 592. Merck does not contend otherwise.

For failure-to-warn claims against brand-name drug manufacturers, the answer is yes: federal law permits manufacturers to strengthen label warnings to comply with state law. Nothing in the FDCA *prohibits* a brand-name manufacturer from changing an approved label. And the CBE regulation specifically authorizes a manufacturer to "chang[e] a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction'" and to do so "upon filing its supplemental application with the FDA; it need not wait for FDA approval." *Levine*, 555 U.S. at 568 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). Thus, when a brand-name manufacturer becomes aware of new information about patients suffering adverse events (or even new analysis of existing data), federal law permits that manufacturer to revise its label accordingly. *See id.* at 569.

In *Levine*, the Court allowed one narrow exception to the general rule that failure-to-warn claims against brand-name drug manufacturers are not preempted. As the Court explained, "FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application." *Id.* at 571. The Court reasoned: "But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.*

In *Mensing*, the Court clarified the nature of the "clear evidence" exception: "the [*Levine*] Court noted that Wyeth could have attempted to show, by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required." 564 U.S. at 624 n.8.

Merck acknowledged below that its preemption defense required showing "there is 'clear evidence' that the FDA would have rejected the addition of the warning that a plaintiff claims was necessary." Pet'r C.A. Br. 31.[14]

C. The 2007 FDCA Amendments Do Not Preempt State Law

The FDAAA did not change *Levine*'s impossibility-preemption analysis. Those amendments gave FDA authority, for the first time, to initiate a process to require manufacturers of approved drugs to change their labels. 21 U.S.C. § 355(*o*)(4). Congress did not add an express preemption clause, nor did it restrict manufacturers' ability to add changes unilaterally through CBE supplements. Rather, Congress enacted a "[r]ule of construction" that FDA's new authority "shall not be construed to affect the responsibility of" the manufacturer "to maintain its label in accordance with existing requirements," including the CBE regulation. *Id.* § 355(*o*)(4)(I). Thus, as the *Levine* Court recognized, the FDAAA "reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval." 555 U.S. at 571.[15]

Merck (at 22, 31-32) and PhRMA (at 4-5) err in arguing that one can infer impossibility where FDA has not (yet) exercised its authority to mandate

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[14] Accordingly, Merck has waived any argument that a lesser showing is required. *See* Supp. Cert. Opp. 4.

[15] Thus, *Levine* itself rejected PhRMA's argument (at 4) that the FDAAA "modif[ies] the preemption equation presented in *Levine*."

a label change. In Merck's view (at 22, 39), FDA has a "statutory obligation" to mandate a label change whenever such a change is scientifically justified, and it would therefore constitute "agency lawlessness" for FDA to rely on a manufacturer to update a label, rather than to mandate a change itself.

Merck's argument is at odds with the statutory text, as well as FDA guidance and practice. The FDAAA confers upon FDA *discretionary* authority to mandate label changes, while "reaffirm[ing] the manufacturer's obligations" to keep its label up to date. *Levine*, 555 U.S. at 571. The statute provides: "If the Secretary [of Health and Human Services] becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall" initiate a process to mandate a label change. 21 U.S.C. § 355(*o*)(4)(A). The Court long has understood this familiar structure — that an executive official *shall* act *if* the official determines that action is warranted — as conferring discretionary authority to determine when to act. For example, in *United States v. George S. Bush & Co.*, 310 U.S. 371 (1940), the Court considered a statute providing that "the President 'shall by proclamation approve [tariff rates] . . . , if in his judgment such rates . . . are . . . necessary to equalize . . . differences in costs of production.'" *Id.* at 376-77. The Court concluded that this statute conferred "discretionary power" on the President, which was "not subject to review." *Id.* at 380.

FDA has issued guidance confirming it regards the authority to mandate label changes as discretionary: "FDA does not anticipate that all labeling changes that may be related to safety will be required and reviewed under [§ 355(*o*)(4)]. For other labeling changes, application holders may continue to submit

labeling supplements using standard procedures," including the CBE regulation.[16]

FDA practice confirms that, following the FDAAA's enactment, the agency has continued to rely on manufacturers to make most label updates, exercising its power to mandate changes only on rare occasions. In the two years following the FDAAA's enactment (through September 14, 2009), FDA required safety-related labeling changes 22 times.[17] During the partially overlapping two-year period of 2009 and 2010, drug manufacturers submitted 363 CBE supplements for the same type of change.[18] Thus, far more label updates resulted from unilateral manufacturer action than FDA mandate.

The reason FDA primarily has relied on manufacturers to make label changes is obvious: "FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge." *Levine*, 555 U.S. at 578-79 (footnote omitted). As Sen. Kennedy explained in his statement regarding the FDAAA's enactment, Merck's annual sales of Fosamax Plus D

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[16] FDA, *Guidance for Industry Safety: Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* 5-6 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

[17] *See* FDA, FDA Implementation – Highlights Two Years After Enactment, https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm184271.htm.

[18] *See* FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products* 7, https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm375128.pdf.

"alone exceed the entire $120 million FDA budget for drug safety," even after that budget was more than doubled by the FDAAA. 153 Cong. Rec. S11,831, S11,832 (daily ed. Sept. 20, 2007).

The FDAAA reaffirmed manufacturers' regulatory duty to keep their labels up to date. It does not insulate manufacturers from liability or authorize them to wait to act until mandated by FDA.[19]

II. MERCK HAS NOT SHOWN BY CLEAR EVIDENCE THAT FDA WOULD HAVE RESCINDED AN ADEQUATE WARNING OF ATYPICAL FEMORAL FRACTURES

Merck failed to show that it was impossible to comply with state law. Merck never attempted to add an adequate warning of atypical femoral fractures, and thus the question of how FDA would have responded to such a warning is hypothetical. When Merck proposed to add a warning that focused on "stress fractures," FDA issued a Complete Response Letter explaining it was rejecting Merck's proposal because of the unsupported discussion of the link between stress fractures and atypical femoral fractures. The additional informal FDA communications (and Merck's self-serving hearsay accounts of those communications) upon which Merck relies are equivocal (at best) and cannot establish preemption. The relevant history — FDA mandated an atypical-femoral-fracture warning soon after a report accurately

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[19] Congress considered and rejected such an approach. The Senate bill that became the FDAAA provided that a manufacturer could not strengthen a label until ordered to do so by FDA. *See* S. 1082, 110th Cong. § 208 (2007). But Congress rejected that provision and "[i]nstead . . . adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Levine*, 555 U.S. at 567-68.

described the fractures, in contrast to Merck's inaccurate "stress fracture" characterization — confirms that Merck *could* have added an accurate atypical-femoral-fracture warning much earlier.

By claiming broad preemption based on a government *amicus* brief and informal agency communications, Merck stretches impossibility preemption beyond the breaking point, advancing a defense that more closely resembles the type of obstacle preemption based on "agency musings" rejected in *Levine*, 555 U.S. at 573-80; *id.* at 587 (Thomas, J., concurring in the judgment).

A. The Complete Response Letter Regarding Merck's Proposed Stress-Fracture Warning Did Not Preclude Merck From Adding An Adequate Warning Of Atypical Femoral Fractures

According to Merck (at 1, 34-35), it proposed a warning "addressing th[e] risk" of "atypical femoral fractures," and, in FDA's Complete Response Letter, "FDA rejected Merck's request to warn about atypical femoral fractures," making it "impossible for Merck to revise its label to conform to the state-law duties that respondents allege."

Every aspect of Merck's factual framing is wrong. Merck never proposed a warning of atypical femoral fractures to FDA. In an attempt to minimize the risk, Merck proposed to warn of "stress fractures," which are widely understood as minor fractures far less serious than atypical femoral fractures. In the Complete Response Letter, FDA explained that it rejected Merck's proposal because Merck's identification and discussion of "stress fractures" did not match the literature on atypical femoral fractures. FDA told Merck it could submit a revised proposal remedying that deficiency. The plain import of the Complete

Response Letter, and its formal legal effect, was to reject Merck's proposed stress-fracture warning. Far from *precluding* Merck from adding an adequate warning of atypical femoral fractures, FDA *invited* Merck to do so.

1. Merck never proposed an accurate warning of atypical femoral fractures

Merck's proposed warning minimized and mischaracterized the risk by focusing on "stress fractures" of the femur, JA707, which are much less serious than the atypical femoral fractures suffered by respondents. The heading and first sentence of Merck's proposal referred to "[l]ow-energy" "femoral shaft" fractures, but did not describe the nature of the fractures adequately or specifically. *Id.* Every sentence after that described the fractures as "stress fractures." *See*, *e.g.*, *id.* (patients experienced pain "often associated with imaging features of stress fracture"; "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate"; "patients with suspected stress fractures should be evaluated including evaluation for known causes and risk factors (e.g., . . . previous stress fracture . . .)"; "[i]nterruption of bisphosphonate therapy in patients with stress fractures should be considered").

Merck's proposed language warned of femoral stress fractures. But a simple comparison of x-rays of an atypical femoral fracture and a femoral stress fracture illustrates the difference. *See supra* pp. 14-15. One looks like a pencil snapped in two. The other is a slight protrusion, barely perceptible to people without radiology training.

Both FDA and Merck have acknowledged the crucial distinction between stress fractures and atypical femoral fractures. In 2010, FDA explained that

characterizing atypical femoral fractures as "stress fractures" would "contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use" because, "for most practitioners, the term 'stress fracture' represents a minor fracture." JA566. In crafting a response, Merck acknowledged internally that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." C.A.App.1573; *see also* JA145-46 (Burr Decl. ¶ 86) (atypical femoral fractures are "much more significant than 'garden-variety' stress fractures").

While in rare cases stress fractures can progress into atypical femoral fractures, Merck's proposed warning "improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome." JA144 (Burr Decl. ¶ 84). As Merck itself acknowledged, the rare stress fractures that can develop into atypical femoral fractures differ from the ubiquitous stress fractures that result from overloading a heavy bone (e.g., through athletic activity). C.A.App.1341. Merck's proposed warning listed "risk factors" for stress fractures that "simply were not associated with AFF," JA142 (Burr Decl. ¶ 79), including "extreme or increased exercise," JA707.

Merck's application also contained a clinical overview that obscured the nature of atypical femoral fractures. JA745-61. The clinical overview failed to "provide the FDA with any possible pathogenesis for AFF from long-term Fosamax," meaning the scientific mechanism through which Fosamax causes atypical femoral fractures. JA136 (Burr Decl. ¶ 69). Merck's overview also erroneously described atypical femoral fractures as similar to fractures suffered by persons

who did not use Fosamax, obscuring that atypical femoral fractures were a rare form of fracture predominantly seen in bisphosphonate users. JA138 (*id.* ¶ 72) (quoting JA755). Merck's protestation (at 35) that it disclosed scientific evidence to FDA thus rings hollow; while Merck disclosed some of the relevant literature, its clinical overview tended to obscure rather than enlighten the meaning of that literature.

This case is similar to *Levine* in that the manufacturer sought preemption based on FDA's rejection of proposed warning language that did not actually address the risk that caused the plaintiff's injuries. In *Levine*, Wyeth and the dissent argued that Ms. Levine's failure-to-warn claims were preempted because Wyeth proposed warning language regarding the risk of intravenous injection of Phenergan, and "FDA rejected Wyeth's proposal." 555 U.S. at 605 n.1 (Alito, J., dissenting). Although Wyeth's proposal addressed intravenous injection generally, it did not warn adequately of the specific dangers of using the IV-push method. *Id.* at 572 & n.5 (majority). The majority therefore rejected Wyeth's and the dissent's argument because Wyeth had not "attempted to give the kind of warning required by the Vermont jury." *Id.* at 572. The same is true here. Merck's proposal described a different type of fracture from those suffered by respondents, and it was not "the kind of warning" that would satisfy Merck's state-law duty to warn.

2. The Complete Response Letter did not preclude Merck from adding an adequate warning of atypical femoral fractures through a CBE supplement

FDA rejected Merck's proposal because of the inaccurate discussion of stress fractures and then

invited Merck to submit alternative language. The Complete Response Letter offered only one reason for rejecting Merck's stress-fracture warning: Merck's identification of the risk as, and discussion of, "stress fractures." FDA's explanation is important because a complete response letter is required to "describe all of the specific deficiencies that the agency has identified in an application." 21 C.F.R. § 314.110(a)(1).

The first sentence of FDA's explanation for rejecting the stress-fracture warning (quoted in full *supra* p. 16) states that Merck's "justification" for its "proposed . . . language is inadequate." JA511. FDA limited its criticism to Merck's "proposed . . . language" regarding stress fractures, not to warnings of atypical femoral fractures. The next sentence explains that the justification for Merck's language was inadequate because "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." *Id.* FDA's critique was not that the "literature" contained insufficient evidence that Fosamax causes atypical femoral fractures; it was that Merck's discussion of "stress fractures" misidentified the nature of the risk shown by the literature. Next, FDA explained that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and postmarketing adverse event reporting." JA511-12. Again, FDA did not note any lack of support in the "available literature" or "postmarketing adverse event reporting" for the notion that Fosamax causes atypical femoral fractures. Rather, what was "not adequately supported" was "[d]iscussion of the risk factors for stress fractures." A warning listing risk factors unrelated to atypical femoral fractures would confuse physicians and patients and make it less likely

they would recognize the risk connecting Fosamax use with an atypical femoral fracture.[20]

Merck's assertion (at 34) that FDA issued a "flat . . . rejection" of any femur-fracture warning also cannot be squared with FDA's invitation to resubmit the application. FDA stated that "we cannot approve these applications *in their present form*." JA511 (emphasis added). It invited Merck "to resubmit" its application after "fully address[ing] all the deficiencies listed," JA512; *see* 73 Fed. Reg. at 39,589 (complete response letters "convey that [FDA] cannot approve an application *in its present form*," while "informing sponsors *of changes that must be made before* an application can be approved, with *no implication* as to the ultimate approvability of the application") (emphases added).[21] Signifying that the process was ongoing, FDA invited Merck to call an FDA regulatory project manager with any questions. JA513. FDA's approach was fully consistent with "the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Levine*, 555 U.S. at 579. In no conceivable understanding of the English language was it "impossible" for Merck to add appropriate warning language.

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[20] *See* JA142 (Burr Decl. ¶ 79) ("When the Task Force examined the actual data, many of the 'risk factors' identified by Merck in its submission to the FDA simply were not associated with AFF.").

[21] In practice, FDA regularly approves resubmitted applications after deficiencies identified in a complete response letter are remedied. *See generally* Theresa Allio, FDAnews, *FDA Complete Response Letter Analysis: How 51 Companies Turned Failure into Success* (2013) (identifying 51 drugs approved from 2009 through 2013 following complete response letters). For 47% of those applications discussed in that study, the manufacturer secured approval after remedying a labeling deficiency identified in the complete response letter. *Id.* at 11-12.

3. The government's *post hoc* interpretations of the Complete Response Letter are implausible and inconsistent with FDA regulations

a. The Complete Response Letter contains not a hint of what Merck (at 49) and the government (at 30-31) now contend was the real reason behind FDA's decision: the supposed lack of scientific evidence that Fosamax causes atypical femoral fractures. Try as they might, neither the government nor Merck can identify any language in the Complete Response Letter citing insufficient evidence of a causal connection between Fosamax and atypical femoral fractures. Instead, FDA cited inadequate scientific support for "[i]dentification of 'stress fractures'" and "[d]iscussion of the risk factors for stress fractures." JA511-12.

Merck's contemporaneous understanding of the Complete Response Letter contradicts its *post hoc* litigation position. The day Merck received the Complete Response Letter, Merck's U.S. Regulatory Liaison James Adams informed his colleagues that FDA "believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures." JA515. Merck's Director of Clinical Research Arthur Santora responded that "FDA wouldn't let us mention stress fractures." JA517. Merck's scientists correctly interpreted FDA's Complete Response Letter; its lawyers have not.

The government argues (at 30-31) that FDA's approval of Adverse Reactions language roughly matching the heading of Merck's proposed Warnings and Precautions language means that FDA intended to reject any Warnings and Precautions language addressing atypical femoral fractures. On the contrary, FDA's action shows it was willing to approve a

warning of low-energy femoral fractures but unwilling to approve language that misidentified atypical femoral fractures as stress fractures. FDA's approval of the Adverse Reactions language in May 2009 thus strongly supports the conclusion that it was possible for Merck to warn of atypical femoral fractures in the Warnings and Precautions section as well, so long as it properly identified and described the risk at issue.

b. Two FDA regulations relied on by Merck (at 32) and the government (at 6, 32) do not support their interpretation of the Complete Response Letter.

First, an FDA regulation provides that, "if the only deficiencies" in an application "concern editorial or similar minor deficiencies in the draft labeling," FDA will approve the application contingent upon specified labeling changes. 21 C.F.R. § 314.105(b). But the deficiencies in Merck's proposed warning were neither editorial nor minor. Merck wholly misdescribed the risk and listed scientifically unsupported risk factors. *See supra* Part II.A.1. Given the magnitude of the deficiencies, FDA reasonably relied on Merck to remedy them in the first instance.

Second, another regulation states that "FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application." 21 C.F.R. § 314.102(b). FDA did so by communicating the deficiencies to Merck in its Complete Response Letter. JA511-12. Moreover, Merck's deficiencies were not easily correctable but rather would have required Merck to rewrite its proposal to address atypical femoral fractures, rather than stress fractures.

The regulation directly on point, governing complete response letters, further undermines Merck's position. Under that regulation, FDA was required to "describe

all of the specific deficiencies" in Merck's application. 21 C.F.R. § 314.110(a)(1) (emphasis added). The letter here did not describe the supposed lack of evidence connecting Fosamax to atypical femoral fractures. Merck's preemption theory thus depends on the premise that FDA submitted a non-compliant Complete Response Letter listing a false reason for denying the application and omitting discussion of the true reason. *See* Pet.App.53a n.135 (Merck's argument depends on supposition that FDA did not "follow[] § 314.110 to a T"). The far more natural inference is that FDA meant what it said: it rejected Merck's proposal because of the unsupported stress-fracture warning.[22]

c. Merck (at 37-38) and the government (at 33) err in analogizing this case to *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018), in which the Seventh Circuit found that claims were preempted based on detailed FDA scientific analysis rejecting a warning. There, GlaxoSmithKline added the type of warning the plaintiff contended was required (suicide risk in older adults) through a CBE supplement, but FDA ordered GlaxoSmithKline to remove the warning

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[22] The government's attempt (at 32) to minimize the complete-description requirement fails. As the government notes (*id.*), one exception exists to this requirement: "If FDA determines, after an application is filed . . . , 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." 21 C.F.R. § 314.110(a)(3). That provision refers to an NDA, not a labeling supplement. In an NDA, where data submitted are inadequate to support approval of the drug (e.g., for failure to demonstrate safety or efficacy), it makes perfect sense for FDA not to inspect manufacturing facilities or review labeling. For an application that solely seeks to amend labeling, however, FDA cannot evaluate adequacy of the "data submitted" without "reviewing proposed product labeling."

based on its "meta-analysis," which "considered 372 placebo-controlled clinical trials and involved nearly 100,000 adult patients," and "concluded that the 'net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64.'" *Id.* at 809; *see Dolin v. SmithKline Beecham Corp.*, No. 1:12-cv-06403, Dkt. 589-14 (N.D. Ill. Sept. 25, 2017) (64-page meta-analysis).[23]

Likewise, in *Cerveny v. Aventis, Inc.*, 855 F.3d 1091 (10th Cir. 2017), the Tenth Circuit found preemption where FDA rejected the warning sought by the plaintiffs in a letter that meticulously analyzed the evidence and picked apart the scientific arguments. *Id.* at 1101; *see* Appellant App. 383-94, *Cerveny v. Aventis, Inc.*, No. 16-4050 (10th Cir. July 11, 2016) (FDA letter). As illustrated by *Dolin* and *Cerveny*, if FDA had concluded in May 2009 that insufficient evidence linked Fosamax to atypical femoral fractures, it would have said so and explained its conclusion in the Complete Response Letter.

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[23] The chronology of FDA's actions in *Dolin* supports respondents' position. There, FDA allowed GlaxoSmithKline to maintain its CBE-added warning for more than a year, before FDA finished studying the issue and directed uniform warnings for the class of drugs, SSRIs, that excluded GlaxoSmithKline's language. *Dolin*, 901 F.3d at 808-09. Here, FDA was actively studying the relationship between bisphosphonates and atypical femoral fractures since no later than June 2008. JA280. FDA's actions in *Dolin* strongly suggest that, had Merck added an atypical-femoral-fracture warning through a CBE supplement while FDA was studying the issue, FDA would not have rescinded it. Rather, FDA would have allowed Merck to maintain the warning until FDA completed its study and decided to mandate that all bisphosphonate manufacturers add atypical-femoral-fracture warnings.

d. In asserting (at 50) that the government's certiorari-stage brief makes this case a "slam dunk," Merck misunderstands that brief. The government's *amicus* briefs in this case are not (as Merck contends at 49-50) a factual representation from FDA that FDA would not have approved a femur-fracture warning before October 2010. Rather, the briefs convey the government's legal argument (which is incorrect for the reasons explained).

In both briefs, the government made clear when it was making specific factual representations regarding FDA's actions.[24] By contrast, the government described its interpretation of the Complete Response Letter as its "conclusion," purportedly based on its reading of the Letter and other regulatory context. U.S. Cert. Br. 19. The merits-stage brief confirmed (at 32) that interpretation to be its "understanding."

Nor is the government's brief entitled to deference. When an agency has enacted a regulation, this Court has given "some weight" to the agency's explanation of the regulation's objectives in determining whether state law obstructs a significant federal objective. *See Geier v. American Honda Motor Co.*, 529 U.S. 861, 883 (2000). But, here, no regulation purportedly preempts state law. *See Levine*, 555 U.S. at 582 (Breyer, J., concurring) (rejecting U.S. brief arguing for preemption in absence of "lawful specific regulations" with preemptive effect); *see also Mensing*, 564 U.S. at 613 n.3 ("[W]e do not defer to an agency's ultimate conclusion about whether state law should be pre-empted.").

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[24] *See* U.S. Cert. Br. 3 n.2 ("FDA has informed this Office [of the Solicitor General]"); *id.* at 5 ("FDA . . . confirmed to this Office"); *id.* at 7 n.6; *accord* U.S. Br. 3 n.2, 5, 7 n.6.

More recently, several Justices have expressed profound skepticism of judicial deference to government litigation briefs setting forth new legal interpretations. *See E.I. Du Pont de Nemours & Co. v. Smiley*, 138 S. Ct. 2563, 2564 (2018) (Gorsuch, J., joined by Roberts, C.J., and Thomas, J., respecting denial of certiorari) (expressing concern that deference to agency litigation briefs may raise "serious equal protection concerns" and could undermine the Administrative Procedure Act "by incentivizing agencies to regulate by *amicus* brief"); *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2481 (2013) (Breyer, J., joined by Kagan, J., dissenting) (refusing to defer to agency views "set forth . . . only in briefs filed in litigation, not in regulations, interpretations, or similar agency work product").

Even if the Court accorded minimal consideration to the government's brief under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), that would make no difference. Under *Skidmore*, the weight of an agency interpretation hinges upon "the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade." *Id.* at 140. Here, the government's brief glossed over the difference between stress fractures and atypical femoral fractures, misinterpreted the plain language of the Complete Response Letter, and ignored FDA regulations, guidance, and practice that cut against the government's litigation position. The Court should reject the government's view, just as it did in *Levine*.

B. Merck's Informal Communications With FDA Do Not Establish Preemption

In its merits brief, Merck dramatically shifted course from its Third Circuit arguments. Here, Merck

argues primarily (at 21-23, 31-40) that the Complete Response Letter preempts respondents' claims. Below, Merck "direct[ed] [the Third Circuit's] attention away from [the Complete Response Letter] and instead toward a series of informal FDA communications from the same time period between Dr. Monroe [of FDA] and Merck." Pet.App.47a. Perhaps recognizing the weakness of its current theory, Merck still relies on these informal communications (at i, 12-13, 34-35) as a fallback. Merck's old theory fares no better than its new one. Its discussion of the informal communications is nothing more than speculation that FDA *might* have rejected an adequate warning. That falls far short of the clear evidence of impossibility this Court's precedents require.

The Merritt memorandum, which Merck touted below as its "single best piece of evidence," Pet.App.49a n.125, does not support preemption.[25] That document purports to summarize a phone call that a Merck employee had with Dr. Monroe, the FDA official who wrote the Complete Response Letter. JA764-67. The memorandum, which refers to "[t]he conflicting nature of the literature," JA767, at best raises factual questions regarding the accuracy of Merritt's notes and the content and meaning of what Dr. Monroe said. If "agency musings" are insufficient to preempt state law, *Levine*, 555 U.S. at 587 (Thomas, J., concurring in the judgment), then surely a regulated party's self-serving hearsay account of such musings cannot suffice.

Merck also relies (at 12-13, 35) on an April 2009 email from FDA to Merck stating that an Adverse Reactions label change could be approved immediately,

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[25] Merck continues to rely on this document. Pet. Br. i, 12, 34.

"[i]f Merck agrees to hold off on the W&P [Warnings and Precautions] language at this time," and that FDA "would then work with . . . Merck to decide on language for a W&P atypical fracture language, if it is warranted." JA508. That document supports respondents. FDA's willingness to "work with" Merck on alternative "W&P atypical fracture language" contradicts Merck's reading of the Complete Response Letter as a definitive rejection of any femur-fracture warning. The Third Circuit correctly concluded that the record supported the inference that "it was Merck's failure to re-submit a revised CBE or PAS without stress-fracture language, rather than the FDA's supposedly intransigent stance on the science, that prevented the FDA from approving a label change." Pet.App.67a.

C. FDA's Decision To Mandate An Atypical-Femoral-Fracture Warning Undercuts Merck's Preemption Defense

FDA's decision to *require* bisphosphonate manufacturers to add an atypical-femoral-fracture warning — expressed in a series of announcements in 2010 — confirms that it was possible for Merck to add an adequate warning.

In March 2010, spurred by "news reports" connecting bisphosphonates to atypical femoral fractures, FDA announced it was working "with outside experts," including the ASBMR Task Force, "to gather additional information." JA519-20.[26] On September

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[26] Merck notes (at 34) FDA stated the data "have not shown a *clear* connection" between bisphosphonates and atypical femoral fractures. JA519 (emphasis added). That statement does not support impossibility preemption because the federal standard for adding a warning is far lower: Merck was permitted (and obligated) to add a warning "as soon as there is reasonable evidence

14, 2010, after the Task Force published its report, FDA announced that the Task Force's "case definition that describes the atypical features of these unusual fractures" would "help greatly" in understanding the issue. JA523. On October 13, 2010, when FDA directed bisphosphonate manufacturers to discuss atypical femoral fractures in the Warnings and Precautions section, FDA explained the Task Force report "summarized" "data . . . regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures." JA249. In a conference call that same day, an FDA official explained the report "helped us understand these fractures a little bit better," JA494, and "helped to clarify the features of atypical femur fractures," JA488.[27]

Thus, FDA did not view the Task Force report as a sea change in the data connecting bisphosphonates to atypical femoral fractures. Instead, the report "summarized" existing data in a way that "clarif[ied] the features of atypical femur fractures," JA249, 488, and that clarification spurred FDA to mandate a warning. Far from showing that FDA would have rejected an atypical-femoral-fracture warning before the report, as Merck (at 34-35) and the government (at 33-34) assert, the context indicates that Merck would have succeeded had it submitted an application that accurately described and warned of atypical femoral

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of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i). Indeed, even when FDA mandated a warning in October 2010, the agency noted it was "not *clear* if bisphosphonates are the cause" of atypical femoral fractures. JA247 (emphasis added).

[27] Dr. Burr, a principal author of the report, confirmed the report presented no new data but merely reviewed and reported on "the currently available information" regarding atypical femoral fractures. JA133-34 (¶ 62).

fractures, rather than conflating them with stress fractures. After all, the Task Force report did little more than clear up the confusion caused by Merck's own stress-fracture proposal.

Finally, Merck's acquiescence to FDA's demand to add a warning removes any doubt about the current state of the science. JA223-24. Merck, respondents, and FDA all agree there is reasonable evidence Fosamax causes atypical femoral fractures. This is not a case where a successful lawsuit could force a manufacturer to over-warn beyond the balance preferred by FDA. *Cf.* PhRMA Br. 22-25 (reiterating rejected concern that tort suits could upset "balance" in drug labeling); *Levine*, 555 U.S. at 579 ("State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly.").

III. THE THIRD CIRCUIT'S GUIDANCE FOR THE DISTRICT COURT ON REMAND WAS CORRECT

In denying summary judgment, the Third Circuit gave guidance to the district court on questions regarding the allocation of fact-finding between the judge and jury, as well as the standard of proof. According to Merck (at 42), the Third Circuit's conclusion that the jury should resolve disputed factual questions has no bearing on whether the Third Circuit's denial of summary judgment should be affirmed, because "the identity of the ultimate factfinder" is distinct from the question "whether any genuine dispute of material fact existed."[28] Merck also describes

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[28] In its invitation brief, the government opined that "the question is close" whether certiorari was warranted, but narrowly recommended certiorari because the "underlying issue" of whether preemption issues should be submitted to "courts" or

(at 40) the Third Circuit's discussion of the standard of proof as "irrelevant" to whether the denial of summary judgment should be affirmed. Respondents agree. This Court may affirm the Third Circuit's denial of summary judgment without reaching those issues. If the Court does reach them, the Third Circuit's approaches are correct.

A. A Jury Should Resolve Disputed Factual Questions Necessary For Preemption

The question whether FDA would have rescinded an adequate atypical-femoral-fracture warning that Merck never proposed is factual, and the Court should adhere to the traditional rule that juries decide factual questions in common-law tort suits.

1. In civil actions at law, judges handle legal questions, while "predominantly factual issues are in most cases allocated to the jury." *Monterey*, 526 U.S. at 720. That allocation "rests on a firm historical foundation," which ultimately derives from the Seventh Amendment. *Id.* at 718, 720. Questions that involve both "legal aspect[s]" and "factual component[s]" are "mixed question[s] of fact and law." *Id.* at 721. It is "proper to submit" the "fact-bound" aspects of such questions to the jury. *Id.*; *see also id.* at 732 (Scalia, J., concurring in part and concurring in the judgment) (separating mixed question into "two subquestions": "a question of law for the court" and "a question of fact for the jury").

That analysis applies equally to factual issues relevant to preemption. In *Boyle*, the Court held that "whether the facts establish the conditions for"

"juries" was "significant." U.S. Cert. Br. 22. Now that Merck has stated (at 40, 42) that the issue is "moot[]" and "there was no need" for the Third Circuit to address it, the basis on which the Court granted certiorari no longer exists.

the government-contractor-preemption defense "is a question for the jury," unless the summary-judgment standard is satisfied. 487 U.S. at 514. The government unpersuasively attempts (at 28-29) to distinguish *Boyle* as involving "factbound showings," unlike this preemption defense. But, under *Boyle*, a jury determines whether government officials had knowledge of dangers of equipment when approving a contract. 487 U.S. at 514. That determination is no more factbound than determining whether FDA officials clearly evinced an intent to reject a hypothetical warning the drug manufacturer never proposed.

Juries routinely determine outcomes in a counterfactual world, such as whether a drug manufacturer has shown, by clear evidence, that FDA would have rejected an adequate warning. In most tort cases, the jury decides causation and damages by comparing a plaintiff's current position to the plaintiff's hypothetical position but for the defendant's tortious actions. *See* Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 26 (2010) ("Conduct is a factual cause of harm when the harm would not have occurred absent the conduct."); Restatement (Second) of Torts § 906 cmt. c (1979) (damages include "loss of prospective earnings based upon the evidence concerning what [plaintiff] probably could have earned but for the harm"). Predicting FDA's response to a hypothetical CBE supplement adding an adequate warning is likewise a counterfactual analysis appropriate for resolution by the jury.

The fact that this preemption question involves assessing actions of government officials for purposes of deciding a constitutional defense does not change that conclusion. This Court and other courts regularly submit such questions to the jury. For example, in

Monterey, the takings claim required assessing whether "the city's decision . . . bore a reasonable relationship to its proffered justifications," which the Court held was properly submitted to the jury. 526 U.S. at 721. Likewise, in First Amendment employment-retaliation cases, juries plumb the motivations of government officials to "find whether the [employee's] discharge was caused by" protected speech. *Id.* at 731 (Scalia, J., concurring in part and concurring in the judgment) (citing *Horstkoetter v. Department of Pub. Safety*, 159 F.3d 1265, 1271 (10th Cir. 1998)). In Fourth Amendment excessive-force cases, the reasonableness of an officer's actions is generally assessed by a jury, unless the evidence is so one-sided that a reasonable jury could reach only one conclusion. *See Scott v. Harris*, 550 U.S. 372, 380-81 & n.8 (2007).

Merck and the government offer no persuasive justification for treating the *Levine* "clear evidence" inquiry any different from other factual questions. The government (at 20-21) and Merck (at 44-45) argue that, even if the preemption issue involves factual questions, the court should be the factfinder. They attempt to analogize to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388-91 (1996), which held that construction of written patent claims is for the court, even if it involves some factual elements. That analogy fails because the question in *Markman* was construction of a written legal document, which traditionally has been allocated to judges. By contrast, the question under the "clear evidence" exception is whether the manufacturer has supported its prediction about FDA's response to a hypothetical CBE supplement with clear evidence, which is the sort

of factual question that courts traditionally submit to juries.

Finally, the specific context of federal drug regulation provides no justification for shielding factual questions from juries. The FDCA assigns to juries the task of assessing the adequacy and accuracy of drug labels in determining whether drugs are misbranded. 21 U.S.C. § 352(a), (f); *see Levine*, 555 U.S. at 570 ("the statute contemplates that federal juries will resolve most misbranding claims"). Neither Merck nor the government articulates any principled reason why juries are competent to handle misbranding claims but not factual questions related to preemption.

2. To be sure, it frequently will be possible for courts to resolve preemption defenses on summary judgment, either for or against preemption, based on an undisputed regulatory record. And the legal effect of a written regulatory action, such as the Complete Response Letter, is a question for the court. Resp. Supp. C.A. Br. 4. But Merck and the government err in contending that the answer to that question justifies preemption here. The Complete Response Letter in this case rejected a stress-fracture warning, not an atypical-femoral-fracture warning. Thus, Merck's defense required showing that FDA would have rejected "a different label amendment than the one it actually rejected in the May 2009 letter." Pet.App.52a.

Respondents argued below, and still believe, that Merck's preemption defense fails as a matter of law because the text of the Complete Response Letter provides no support for Merck's contention that FDA had rejected *any* femur-fracture warning. Resp. Supp. C.A. Br. 4. Yet the Third Circuit concluded that jury resolution was required because "Merck . . . direct[ed]

[the Third Circuit's] attention away from [the Complete Response Letter] and instead toward a series of informal FDA communications" that purportedly revealed FDA's true intentions. Pet.App.47a; *see also* Pet'r C.A. Br. 40-48, 50-53 (relying on informal FDA statements). Merck relies (at 34-35) on those informal communications (including the Merritt memorandum[29]) not to interpret the Complete Response Letter, as the government suggests (at 27), but to furnish a basis for preemption not found in that Letter. Although Merck asserts (at 36-37) that the Third Circuit erred by treating the Complete Response Letter as "simply one piece of evidence for the jury to consider" along with informal FDA communications, Merck *invited* that approach.

The Third Circuit correctly recognized that Merck's preemption theory implicated "credibility determination[s]" of Merritt and required "weigh[ing] . . . competing inferences" about Dr. Monroe's intent in light of supposed conflicts between FDA's official regulatory action and informal communications. Pet.App.49a n.125. Those "are precisely the types of personal evaluations and weight-of-the-evidence assessments that [courts] commit to jurors in the first instance." *Id.*

B. The Third Circuit Correctly Required A Heightened Standard Of Proof For Impossibility Preemption Under *Levine*

A manufacturer must satisfy a heightened standard of proof to qualify for *Levine*'s "clear evidence" exception. As the Court explained in *Mensing*, the exception requires a manufacturer "to *show, by 'clear*

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[29] Merck's quotation regarding "conflicting" literature is from the Merritt memorandum. *Compare* Pet.App.17a *with* JA766-67.

evidence,' that the FDA would have rescinded any change in the label." 564 U.S. at 624 n.8 (emphasis added). The Court's identification of "clear evidence" as the nature of the "show[ing]" required is consistent with a heightened standard of proof.

Such a heightened standard is justified because the "clear evidence" exception recognized in *Levine* stretches the bounds of impossibility preemption. Impossibility preemption typically applies "where it is 'impossible for a private party to comply with both state and federal requirements.'" *Id.* at 618 (quoting *Freightliner*, 514 U.S. at 287). But the FDCA and the CBE regulation make it "physically possible" for brand-name drug manufacturers "to provide stronger warnings." *Levine*, 555 U.S. at 591 (Thomas, J., concurring in the judgment). The "clear evidence" defense depends on a supposition that, *if* the manufacturer complies with state law, a federal agency will take action *in the future* that will prevent the manufacturer from continuing to comply with state law. Because "the possibility of impossibility" is "not enough" for preemption, *Mensing*, 564 U.S. at 624 n.8, a manufacturer must present a particularly compelling showing to trigger preemption under the "clear evidence" exception.

In any event, because it is undisputed that a clear showing is required, *see supra* p. 31 & n.14, it makes no difference whether such a showing is equivalent to the clear-and-convincing-evidence standard of evidentiary proof. The government contends (at 26) that, in the preemption context, "clear evidence" "reflect[s] an *interpretive* presumption against preemption." For its part, Merck concedes (at 46) that "courts should not lightly assume that the FDA would have rejected a proposed warning." It is hard to imagine a case that

would turn on whether the defense requires proof by clear-and-convincing evidence, or evidence sufficient to overcome an "interpretive presumption against preemption." Given Merck's feeble evidentiary showing, this case certainly does not. *See supra* Part II.

C. Granting Summary Judgment Would Violate Respondents' Procedural Rights

In all events, the district court's judgment could not be affirmed without considering respondents' challenge to that court's extraordinary decision to grant an order to show cause why all respondents' claims were not preempted on the basis of the *Glynn* advisory opinion.

Summary judgment must "be refused where the nonmoving party has not had the opportunity to discover information that is essential to his opposition." *Anderson*, 477 U.S. at 250 n.5. Here, the district court granted summary judgment after issuing a show-cause order giving respondents just 45 days to mount evidence in opposition to preemption. JA86-88.[30] The district court's conclusion (at Pet.App.136a) that such a compressed time frame was sufficient because the Glynns had the opportunity to brief preemption on a normal schedule was erroneous. Respondents were not parties in *Glynn*, and Ms. Glynn, who the jury found did not suffer an atypical femoral fracture, JA45, was hardly an adequate representative to litigate the viability of respondents' claims. Denying respondents a chance to gather evidence on the basis of *Glynn*, and applying the *Glynn* ruling against respondents with minimal analysis, violates "the

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[30] *See* JA91 (attorney declaration that 45-day window did not allow "the overwhelming majority of these Plaintiffs to pursue any case specific discovery" and that respondents would have gathered more evidence "if additional time had been provided").

'deep-rooted historic tradition that everyone should have his own day in court.'" *Taylor v. Sturgell*, 553 U.S. 880, 892-93 (2008) (quoting *Richards v. Jefferson Cty.*, 517 U.S. 793, 798 (1996)). The fact that *Glynn* was an MDL bellwether case does not mitigate that unfairness because a bellwether trial is not a "'representative' proceeding." Eldon E. Fallon et al., *Bellwether Trials in Multidistrict Litigation*, 82 Tul. L. Rev. 2323, 2332 (2008).[31]

Subsequent proceedings have starkly demonstrated the prejudice suffered by respondents. As Merck argued on appeal, its "single best piece of evidence" is the Merritt memorandum. Pet.App.49a n.125; JA764-67. Yet respondents have not had the opportunity to depose Merritt to test her credibility or the veracity of her notes.[32]

Although the Third Circuit did not need to reach respondents' objections to the show-cause procedure, the district court's judgment could not be upheld without addressing the procedural infirmities in the district court's approach.

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[31] *See also* Martin H. Redish & Julie M. Karaba, *One Size Doesn't Fit All: Multidistrict Litigation, Due Process, and the Dangers of Procedural Collectivism*, 95 B.U. L. Rev. 109, 126 (2015) (bellwether trials "are not binding on other parties in the MDL").

[32] More than 200 respondents were injured after the May 2009 Complete Response Letter, and some as late as September 2010. MDL Dkt. 2857-2. Those respondents could argue that, even if the Court accepts Merck's contentions regarding the Complete Response Letter, Merck could have warned of atypical femoral fractures at some point after the Complete Response Letter, but soon enough to prevent their injuries. However, the district court's schedule did not permit the type of plaintiff-specific discovery (e.g., when the warning would have been heeded) necessary to develop such an argument.

* * *

Federal law made it possible for Merck to comply with its state-law duty to warn adequately of atypical femoral fractures through a CBE supplement. Neither FDA's rejection of a very different stress-fracture warning, nor the informal FDA communications cited by Merck, established the clear evidence of impossibility required by this Court's precedents.

CONCLUSION

The judgment of the Third Circuit should be affirmed.

Respectfully submitted,

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ADDENDUM

TABLE OF CONTENTS

1. The Supremacy Clause of the U.S. Constitution, art. VI, cl. 2, provides:

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

2. 21 U.S.C. § 331 provides, in relevant part:

§ 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

* * *

3. 21 U.S.C. § 352 provides, in relevant part:

§ 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

(a) False or misleading label

(1) If its labeling is false or misleading in any particular. Health care economic information provided to a payor, formulary committee, or other similar

entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement, shall not be considered to be false or misleading under this paragraph if the health care economic information relates to an indication approved under section 355 of this title or under section 262(a) of title 42 for such drug, is based on competent and reliable scientific evidence, and includes, where applicable, a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug under section 355 of this title or under section 262 of title 42. The requirements set forth in section 355(a) of this title or in subsections (a) and (k) of section 262 of title 42 shall not apply to health care economic information provided to such a payor, committee, or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request.

(2)(A) For purposes of this paragraph, the term "health care economic information" means any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention.

(B) Such term does not include any analysis that relates only to an indication that is not approved under section 355 of this title or under section 262 of title 42 for such drug.

* * *

4. 21 U.S.C. § 355 provides, in relevant part:

§ 355. New drugs

(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) 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). 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. The applicant shall file with the application the patent

number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

* * *

(*o*) Postmarket studies and clinical trials; labeling

(1) In general

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

(2) Definitions

For purposes of this subsection:

(A) Responsible person

The term "responsible person" means a person who—

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

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

(B) Covered application

The term "covered application" means—

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

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

(C) New safety information; serious risk

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

* * *

(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.

(G) Violation

If the responsible person or the holder of the approved application under subsection (j) has not submitted a supplement within 15 days of the date of such order under subparagraph (E), and there is no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) Public health threat

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

(I) Rule of construction

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

* * *

5. 21 U.S.C. § 360k provides, in relevant part:

§ 360k. State and local requirements respecting devices

(a) General rule

Except as provided in subsection (b), no State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement—

(1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and

(2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.

* * *

6. Section 202 of the Drug Amendments of 1968, Pub. L. No. 87-781, 76 Stat. 780, 793, provides:

Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

7. 21 C.F.R. § 201.57 provides, in relevant part:

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

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).

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

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

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

* * *

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

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

* * *

(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) *2 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) *5 Warnings and precautions.* (i) *General.* This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance

with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

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

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

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

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

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

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

(A) *Clinical trials experience*. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse

reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

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

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

* * *

(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 (81⁄2 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.

8. 21 C.F.R. § 314.3 provides, in relevant part:

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part and part 320 of this chapter.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

* * *

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

* * *

9. 21 C.F.R. § 314.70 provides, in relevant part:

§ 314.70 Supplements and other changes to an approved NDA.

(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.

* * *

10. 21 C.F.R. § 314.71 provides:

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

(a) Only the applicant may submit a supplement to an application.

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

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

11. 21 C.F.R. § 314.102 provides, in relevant part:

§ 314.102 Communications between FDA and applicants.

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

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

managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

12. 21 C.F.R. § 314.105 provides, in relevant part:

§ 314.105 Approval of an NDA and an ANDA.

* * *

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

* * *

13. 21 C.F.R. § 314.110 provides:

§ 314.110 Complete response letter to the applicant.

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

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

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

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

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

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

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

(i) A resubmission of an application or efficacy supplement that FDA classifies as a Class 1 resubmission constitutes an agreement by the applicant to start a

new 2-month review cycle beginning on the date FDA receives the resubmission.

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

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

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

(v) A minor resubmission of an abbreviated application constitutes an agreement by the applicant to start a new review cycle beginning on the date FDA receives the resubmission.

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

(3) *Request opportunity for hearing.* Ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively. The applicant must submit the request to the Associate Director for Policy, Center for Drug

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

(c) *Failure to take action.* (1) An applicant agrees to extend the review period under section 505(c)(1) or (j)(5)(A) of the act until it takes any of the actions listed in paragraph (b) of this section. For an application or abbreviated application, FDA may consider an applicant's failure to take any of such actions within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application, unless the applicant has requested an extension of time in which to resubmit the application. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application should not

be withdrawn and to request an extension of time in which to resubmit the application. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application will be deemed to be withdrawn.

14. 21 C.F.R. § 314.125 provides, in relevant part:

§ 314.125 Refusal to approve an NDA.

(a) The Food and Drug Administration will refuse to approve the NDA and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying approval of the NDA under section 505(d) of the Federal Food, Drug, and Cosmetic Act, if:

(1) FDA sends the applicant a complete response letter under § 314.110;

(2) The applicant requests an opportunity for hearing for a new drug on the question of whether the NDA is approvable; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(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.

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