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 OF MEDSHADOW AND FORMER FDA OFFICIALS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE

MedShadow Foundation is an independent, not-for-profit organization whose mission is to ensure people have access to independent information on the side effects and adverse events of medicines in order to balance the benefits and the harms of medicines. MedShadow provides clear, evidence-based information to help people better understand the harms and benefits of the medicine they are taking or may be prescribed so that they can take a more active role in their healthcare. The organization's goal is to save lives by minimizing the harm caused by, and decreasing the unnecessary use of, medicines.

Joshua M. Sharfstein M.D. served as the Principal Deputy Commissioner at the Food and Drug Administration ("FDA") from March 2009 until January 2011. Mary K. Pendergast J.D., LL.M., served as Deputy Commissioner and Senior Advisor to the Commissioner at FDA from November 1990 until December 1997 and as Associate Chief Counsel for Enforcement in the Office of the General Counsel from July 1979 until November 1990. Jeremy Sharp served as the Deputy Commissioner for Policy, Planning, Legislation and Analysis from June 2015 until January 2017. Dr. Sharfstein, Ms. Pendergast, and Mr. Sharp are experts in the regulatory procedures applicable to drugs.[1]

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[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae*, its members, or its counsel made a monetary contribution to its preparation or submission.

INTRODUCTION

Respondents in this case are patients who allege that petitioner's drug, Fosamax (alendronate sodium), caused them to suffer atypical femoral fractures ("AFFs"), which are incapacitating fractures that result from little or no trauma in which the thigh bone, or femur, often breaks in two. J.A. 288-89, 292. Fosamax belongs to a class of drugs called "bisphosphonates," which are commonly used to treat osteoporosis. J.A.192; Pet'r App. 5a. Respondents claim, among other things, that petitioner Merck Sharpe & Dohme Corp. ("Merck) failed to warn of AFFs, which respondents contend was required by state law. Merck argues that it sought to add such a warning, that the Food and Drug Administration ("FDA") in a final irreversible decision rejected that warning, and that, because federal law prohibited it from warning about AFFs until October 2010, respondents' claims are preempted by federal law. Pet'r Br. at 31, 34.

Merck's argument that respondents' claims are preempted turns on: whether Merck ever requested that FDA allow Merck to add a warning for AFFs; whether FDA ever rejected such a request; and whether Merck could have added the warning to its label without waiting for FDA approval or requested FDA's authorization to do so. This brief will demonstrate that a review of the FDA record shows that while Merck did seek to add a warning regarding "low energy femoral shaft fractures" and specifically "stress fractures," which are more common and less severe than AFFs, it never attempted to add a warning for AFFs, and that FDA never made a decision that would have barred Merck

from adding a warning about AFFs to its label with or without waiting for FDA approval.

BACKGROUND

FDA approved Fosamax in 1995 to treat osteoporosis and in 1997 to prevent osteoporosis. Pet'r App. 5a, 12a-13a. Between 1999 and 2002, Merck received adverse event reports indicating that long-term Fosamax users were suffering from atypical femoral fractures. J.A. 122-25 (Burr Decl. ¶¶ 45-50). In 2005, Merck received a report from an orthopedic surgeon of 25 patients who had taken Fosamax for "a long time" and suffered long bone fractures with features consistent with AFFs (although they were not specifically designated as AFFs), noting that in his hospital they call such a fracture the "Fosamax Fracture." J.A. 126-27 (Burr Decl. ¶ 52); J.A. 448. In 2006, a Merck employee in Singapore reported that she had learned of eight cases of atypical femoral fractures suffered by long-term Fosamax users and suggested that those events "might be a signal for a label update." J.A. 452, 455-56. As the Third Circuit summarized, "[b]etween 1995 and 2010, scores of case studies, reports and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." Pet'r App.13a.

In June 2008, FDA sent Merck an information request titled: "Fosamax Information Request – Atypical Fractures." J.A. 280-81. FDA stated that it was "concerned about this developing safety signal" and it requested Merck to submit any investigations it had conducted "regarding the occurrence of atypical fractures with bisphosphonate use," any investigational

plans, and all hip and femoral fracture case reports that the company had received. *Id.* Shortly thereafter, Merck submitted the information FDA had requested. Pet'r App.14a.

Under the Federal Food, Drug and Cosmetic Act ("FDCA"), Merck could also have added a warning about atypical femoral fractures to its label in one of two ways. FDA's changes being effected ("CBE") regulation provides that when a manufacturer becomes aware of new information about serious adverse effects of a drug, it may revise its label to "'add or strengthen a contraindication, warning, precaution, or adverse reaction,' without waiting for FDA approval." *Wyeth v. Levine,* 555 U.S. 555, 569 (2009) (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). Alternatively, the manufacturer may submit a prior approval supplement ("PAS") to FDA seeking a labeling change, which requires it to wait for FDA authorization prior to changing its labeling. 21 C.F.R. § 314.70(b).

Merck did not use either option to add a warning about atypical femoral fractures. Instead, in September 2008 it submitted prior approval supplements for each of its Fosamax products proposing to add language about "low-energy femoral shaft fracture," a broad category that includes AFFs and less serious fractures. J.A. 510-12. Specifically, the warning would have stated that: "[l]ow -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." There was no

mention in Merck's proposed warning of atypical femoral fractures. J.A. 707.

In May 2009, FDA sent a Complete Response Letter ("CRL") to Merck stating that the agency could not approve Merck's PAS applications "in their present form." J.A. 510-13. A complete response letter is the letter FDA sends when it has determined that it will not approve an application or a supplement to an application in its present form. 21 C.F.R. §§ 314.110(a), 314.71. FDA explained that "[w]hile the Division agrees that atypical and subtrochanteric fractures should be added to the Adverse Reactions, Post-Marketing Experience subsections of the . . . labels, your justification for the proposed Precautions section language is inadequate." J.A. 511 (capitalization and bold omitted).[2] According to FDA, "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been

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[2] Under FDA's regulations, there is a significant distinction between what is added in the Adverse Reactions/Post-Marketing Experience sections of the label and what is added to the Warnings and Precautions section. The Adverse Reactions/Post-Marketing Experience sections contain a laundry list of adverse reactions reported that are "reasonably associated with use of a drug." 21 C.F.R. § 201.57(c)(7). On the other hand, an addition to the Warnings and Precautions section must meet the higher standard of "reasonable evidence of a causal association between the drug and the adverse event." 21 C.F.R. § 201.57(c)(6). This section is "intended to identify and describe a discrete set of adverse reactions that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management." U.S. FOOD & DRUG ADMIN, WARNINGS, PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNING SECTIONS OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – CONTENT AND FORMAT: GUIDANCE FOR INDUSTRY 3 (2011).

reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." J.A. 511-12. FDA informed Merck that it could "resubmit" its application. J.A. 512. In July 2009, Merck withdrew its PAS applications and added the approved femur fracture language only to the laundry list of Adverse Reactions in that section of the Fosamax label. J.A. 654-60. There was no mention of atypical femoral fractures. *Id.*

In rejecting Merck's application for a warning about stress fractures, FDA did not decide whether a warning about atypical femoral fractures was warranted. This issue was still under consideration as demonstrated by an email that an FDA employee had sent Merck just a month earlier. In that communication, FDA informed Merck that the Agency was interested in "work[ing] with . . . Merck to decide on language for a [Warnings and Precautions] atypical fracture language, if it is warranted." J.A. 508. There is no evidence that Merck ever followed up on FDA's invitation to work on a warning about atypical fractures or that it ever proposed such a warning to FDA. Nor did Merck exercise its authority under the CBE regulation to add a warning about atypical femoral fractures, which it could have done without awaiting FDA approval.

In 2009, the American Society for Bone and Mineral Research empaneled a task force (the "Task Force"), to address the issue of AFFs primarily in patients who had been taking bisphosphonates for a long period of time. J.A. 133. On September 14, 2010,

the Task Force published its report entitled "Atypical Subtrochanteric and Diaphyseal Femoral Fractures" (the "Task Force Report"). J.A. 283. The Task Force Report concluded that use of bisphosphonate, including Fosamax, increases the risk of atypical femoral fractures. *Id.* Less than a month later, on October 13, 2010, FDA announced that it would require bisphosphonate labeling to include a warning "describing the risk of atypical fractures of the thigh." J.A. 246. On that same day, FDA directed Merck to add three specifically worded paragraphs describing atypical femur fractures to the Warnings and Precautions section. J.A. 526-29.

Consistent with the PAS it had submitted two years earlier, Merck resisted the FDA drafted warning about atypical femoral fractures. Instead it proposed revised language that added five references to "stress fractures," including the language relating to risk factors for stress fractures that Merck had proposed and FDA had rejected in 2009. J.A. 606-07. FDA rejected each of Merck's proposed references to stress fractures and required a warning about atypical femoral fractures, explaining that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." J.A. 566.

ARGUMENT

Under the FDCA and FDA's implementing regulations, a drug manufacturer bears the responsibility for the content of its label at all times.

Wyeth v. Levine, 555 U.S. at 570-77; 21 C.F.R. § 201.56 (a)(2); 21 C.F.R. § 201.57(c)(6)(i); *see also* 21 U.S.C. § 355(o)(4)(I). FDA's regulations require a manufacturer to update its labeling "when new information becomes available that causes the label to become inaccurate, false or misleading." 21 C.F.R. § 201.56(a)(2). Updated warning information must be added "as soon as there is reasonable evidence 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). FDA relies on manufacturers to make label changes because "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." *Wyeth v. Levine*, 555 U.S. at 578-79.

Merck did not ask FDA to add a warning to the Fosamax label about atypical femoral fractures and FDA did not decide whether such a warning would be appropriate. Even if the Complete Response Letter that FDA issued in May 2009 had denied a request for a warning label about AFFs, and it did not, Merck was always free to resubmit its application (addressing the deficiencies identified by FDA in its CRL) or to ask for reconsideration by requesting a hearing on the question of whether there were grounds for denying the labeling change. 21 C.F.R. § 314.110(b). It also had the authority to use the CBE regulation and to add a warning about AFFs, which then FDA would have evaluated based on existing data or new analysis of that data.

I. Merck Did Not Request a Warning for Atypical Femoral Fractures.

In September 2008, Merck submitted a prior approval supplement proposing to add specific language to the Warnings and Precautions section of the Fosamax labeling. That language contained no reference to atypical femoral fractures. Instead the new warning language would have referred to "low-energy fractures of the subtrochanteric femoral shaft" (the upper part of the femur) and then it would have mentioned "stress fractures" six times. J.A. 707.[3] A low energy fracture is a broad term that encompasses a range of fractures, including both atypical femur fractures and stress fractures. J.A. 466; J.A. 109, 139 (Burr Decl.¶¶ 22,73). The term "low energy fracture" is not a red flag because

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[3] The full text of the proposed warning was as follows:

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.

some low energy fractures, such as stress fractures, are relatively common and less medically significant than others, including AFFs. J.A. 139-41 (Burr Decl. ¶¶ 73-75.) Thus, this term does not specifically identify AFFs and the proposed language was not a warning for this very serious type of 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." J.A. 144 (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." J.A. 145-46 (*id.* ¶ 86). As FDA explained in an email rejecting Merck's proposed changes to its 2010 warning, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." J.A. 566. Merck itself has recognized 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." Ct. Appeal App.1573.

According to Dr. David Burr, a co-chair of the Task Force and one of the primary authors of the Task Force Report, Merck's proposed warning "improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome." J.A. 144 (Burr Decl. ¶ 84). Merck's proposed warning also

conflated the rare type of stress fracture that can develop into AFFs with typical stress fractures. According to Dr. Burr, Merck's proposed warning listed "risk factors" for stress fractures that "simply were not associated with AFF," including "extreme or increased exercise." J.A. 142 (Burr Decl. ¶ 79); J.A. 707. In other words, "Merck was attempting to confound the true nature of the association between Fosamax and AFFs." J.A. 143 (Burr Decl. ¶ 81).

Although Merck requested a warning about stress fractures, which FDA concluded was not supported by available data, it never attempted to add a warning for AFFs.

II. The Complete Response Letter Demonstrates that FDA Did Not Reject a Warning for AFFs.

In May 2009, Dr. Scott Monroe, the Director of the FDA Division of Bone, Reproductive and Urologic Products, sent the Division's decision, or Complete Response Letter, to Merck, rejecting its proposal to warn of femur fractures that Merck referred to as "low energy femoral shaft fractures" and "stress fractures." In the CRL, Dr. Monroe explained that "[w]hile the Division agrees that atypical and subtrochanteric fractures should be added to the Adverse Reactions, Post-Marketing Experience subsections of the . . . labels, your justification for the proposed precautions section language is inadequate." J.A. 511. (Capitalization and bold omitted.) According to Dr. Monroe, "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." *Id.* "Discussion of the risk factors for stress fractures is not warranted and is not

adequately supported by the available literature and post-marketing adverse event reporting." J.A. 511-12.

In other words, FDA rejected Merck's request to add a Warning about stress fractures. It could not and did not reject a warning regarding AFFs, because Merck had never asked for one. Nothing in the Complete Response Letter supports what Merck and the Solicitor General contend was the reason behind FDA's decision: a finding by FDA that there was a lack of scientific evidence that Fosamax caused atypical femoral fractures. *See* Pet'r Br. at 49; Solicitor Gen. Br. at 30-31.

A close examination of the CRL demonstrates the flaws in Merck and the Solicitor General's argument. The first sentence of the CRL states that Merck's "justification" for its "proposed ... language is inadequate." 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." In other words, FDA had been concerned about atypical femoral fractures reported in the literature. Rather than request permission to give a warning about those fractures, Merck had sought a warning about stress fractures, for which FDA found that there was insufficient literature support. Again, the CRL did not state that there was insufficient evidence to support an association between Fosamax and atypical femoral fractures. According to the CRL, the only thing that was "not adequately supported" was "[d]iscussion of the risk factors for stress fractures." FDA's conclusion was consistent with the subsequent findings of the ASMBR Task Force that "many of the 'risk factors' identified by

Merck in its submission to the FDA simply were not associated with AFF." J.A. 142 (Burr Decl. ¶ 79).

FDA's issuance of the CRL denying Merck's request for a warning about stress fractures in May 2009 complied with the decision date for responses to PASs established under the Prescription Drug User Fee Act.[4] On the other hand, there was no decision date for deciding on a warning about AFFs because Merck had not submitted a PAS requesting such a warning, and FDA often takes a long time to resolve this type of issue. That FDA had not decided whether a warning about AFFs would be appropriate is confirmed by an April 15, 2009 email from Karl Stiller, FDA Regulatory Project Manager, Division of Bone, Reproductive and Urologic Products, to Merck, regarding a recent discussion that Merck had had with Dr. Monroe (the author of the CRL) and Dr. Kehoe, a Medical Officer and Team Leader in the Division. The email stated that FDA was interested in "work[ing] with ... Merck to decide on language for [Warnings and Precautions] atypical fracture language, if it is warranted." J.A. 508. Written just a month before the CRL, and probably at a time when the substance of the CRL had been decided, this email was an invitation to Merck to work with FDA to agree on language that warned about AFFs.

The Solicitor General states in one of the headings in his brief that "FDA's May 2009 Decision

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[4] U.S. FOOD & DRUG ADMIN., FY 2008 PERFORMANCE REPORT TO THE PRESIDENT AND THE CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT (2008), https://wayback.archive-it.org/7993/20170113075401/http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM209479.pdf.

Rejected A Change To Fosamax's Warnings And Precautions Because The Data At That Time Was Insufficient To Justify A Change." Solicitor Gen. Br. at 30 (capitalization in original). He then asserts that "FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures was based on the agency's determination that the information about that risk was then insufficient to justify such a warning." *Id.* Both these statements are rebutted by the warning that Merck actually proposed which mentioned stress fractures six times but did not contain a single reference to AFF. *See supra* p. 9 n.3. As the email from the FDA official to Merck demonstrates, FDA had not decided the AFF issue and had attempted to work with Merck on a warning about AFFs if one was warranted.

In October 2010, following publication of the Task Force Report, FDA required Merck to add a warning on Fosamax labeling about the risk of atypical femoral fractures. When FDA offered Merck the opportunity to comment on the warning about AFFs, Merck proposed revised language that added five references to "stress fractures," including the language relating to risk factors for stress fractures that Merck had proposed and FDA had rejected in 2009. J.A. 606-07. FDA sent Merck a redline striking out each reference to stress fractures. *Id.*

In their response to FDA, Merck's representatives 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." Ct. Appeal App.1573. As Dr. Burr explained, 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." J.A. 145-46 (Burr Decl. ¶ 86).

The text of the CRL demonstrates that it was not, as Merck contends, a "flat ... rejection" of any femur fracture warning. Pet'r Br. at 34. In fact, FDA stated: "we cannot approve these applications *in their present form*." J.A. 511 (emphasis added). FDA invited Merck "to resubmit" its application and to call an FDA regulatory project manager with any questions, J.A. 512-13, and it had previously informed Merck that it would like to work with the company on crafting a warning about AFFs. Thus, the CRL did not preclude Merck from adding an adequate warning of atypical femoral fractures through resubmission of its PAS. Nor did it preclude Merck from adding an AFF warning via the CBE process, after which FDA would have decided whether it was supported by the data. Merck did neither.

III. Merck Could Have Added a Warning about AFFs Between May 2009 and September 2010 or Submitted a PAS Requesting that FDA Approve a Warning.

As discussed at page 3, *supra,* Merck started to receive adverse event reports suggesting problems with AFFs long before it submitted its PAS application in 2009. In June 2005, Merck performed an internal statistical analysis of Fosamax adverse event reports

and concluded that, as early as 2003, these reports revealed a statistically significant incidence of femur fractures. Ct. Appeal App. 1272-73, 1407, 1443. Respondents' expert biostatistician, David Madigan, confirmed that in 2005 FDA's adverse event database for Fosamax showed a statistically significant signal of a relationship between Fosamax and femur fractures. J.A. 189-92. In 2006, a Merck employee reported that she had learned of femoral fractures suffered by long-term Fosamax users and suggested that those events "might be a signal for a label update." J.A. 452, 455-56.

Likewise, numerous published scientific studies documented the connection between bisphosphonates and atypical femoral fractures. For example, a 2004 article discussed several Fosamax patients who had suffered atypical femoral fractures and concluded that "[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, non-spinal fractures." J.A. 416. A 2008 article published a study of 25 Fosamax users who had suffered atypical femoral fractures, concluding that such fractures were "associated with alendronate use." J.A. 385.

Dr. David Burr, the co-chair of the Task Force, which issued the 2010 report, has confirmed that the Task Force did not conduct any additional research; it based its report on its "review" of "the currently available information," most of which was "available before May of 2009". J.A. 133-34 (Burr Decl. ¶¶ 62, 64). Specifically, the Report summarized what was known at the time about the relationship between bisphosphonates and atypical femoral fractures. Of

the 37 published cases reported and relied on by the task force, 19 were available to Merck by the time it submitted its PAS applications in May 2009. Of the 177 published or available articles and posters cited by the Task Force Report, 120 were available before 2009. J.A. 134 (Burr Decl.¶ 64).

Finally, the fact that FDA mandated an atypical femoral fracture warning soon after the Task Force Report accurately described the fractures suggests that Merck could have added an accurate atypical femoral fracture warning much earlier. As recounted in the Solicitor General's brief, after FDA announced that it was requiring a warning about AFFs on Fosamax and other bisphosphonates, "FDA's Deputy Director for the Office of New Drugs explained that the data that FDA had previously reviewed was insufficient to allow the agency to 'tease out the association between [Fosamax and similar products] and these rare atypical fractures,' but that the task force's September 2010 report had helped FDA 'understand the[] fractures' better." Solicitor Gen. Br. at 11. The FDA official also stated that the Task Force Report "helped . . . make us confident that this is something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for." J.A. 494.

As previously noted, FDA relies on manufacturers to make label changes because "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." *Wyeth v. Levine*, 555 U.S. at 578-79. Merck had access to most

of the data and studies that the Task Force used in its analysis and thus could have applied the analysis used by the Task Force to assist FDA in understanding the data on AFFs. In other words, Merck could have resubmitted its PAS (as FDA suggested) or submitted a CBE and changed its label even sooner. As discussed below, there is no evidence that FDA would have rejected a properly worded warning about AFFs.

IV. Even If FDA Had Rejected a Request by Merck to Warn of the Risk of AFFs, the Task Force Report and FDA's Response Demonstrate that with Appropriate Analysis of Existing Data Merck Could Have Added a Warning about AFF.

FDA's October 2010 decision to require bisphosphonate manufacturers to add an atypical femoral fracture warning after the Task Force had submitted its report demonstrates that Merck likely would have been successful had it in 2009 resubmitted its PAS or unilaterally added an adequate warning. FDA's actions prior to that time also support the conclusion that it would not have rejected a properly worded warning.

In March 2010, following news reports about the risk of AFFs in patients using bisphosphonates, FDA announced that it was "working closely with outside experts, including members of the recently convened [ASBMR] Task Force, to gather additional information." J.A. 519-20.[5] On September 14, 2010, just one month

[5] Merck notes that FDA stated that "the data . . . reviewed have not shown a clear connection between bisphosphonates . . .

after the Task Force published its report, FDA announced that the Task Force's "case definition that describes the atypical features of these unusual femur fractures," would "help greatly" in identifying cases and understanding the risk. J.A. 523. FDA noted that it was considering the Task Force's recommendation that product labels alert health care professionals to the possibility of AFF. J.A. 524. Just one month later, on October 13, 2010, FDA directed bisphosphonate manufacturers to include information about atypical femoral fractures in the Warnings and Precautions section. J.A. 246. FDA noted that the Task Force Report summarized data regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures. J.A. 249.[6]

In a media call on that same day, FDA's Deputy Director for the Office of New Drugs explained that the report "helped us understand these fractures a little bit better," J.A. 494, and "helped to clarify the features of atypical femur fractures." J.A. 488. All of these pronouncements demonstrate that FDA did not view the Task Force Report as providing new data connecting

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and . . . atypical femoral fractures." Pet'r Brief at 13; J.A. 519. The standard for adding a warning, however is not a "clear connection" but rather "as soon as there is reasonable evidence 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). It was at this point that Merck was obligated to change its labeling. Indeed, even when FDA mandated a warning in October 2010, it stated that it was "not clear if bisphosphonates are the cause" of atypical femoral fractures. J.A. 247.

[6] Dr. Burr, co-chair of the Task Force and a principal author of the report, confirmed that the report presented no new data but merely reviewed and reported on "the currently available information" regarding atypical femoral fractures. J.A. 133-34.

bisphosphonates to atypical femoral fractures but rather a summary of existing data that "clarif[ied] the features of atypical femur fractures", and this clarification was sufficient to lead FDA to mandate a warning. J.A. 249, 488. As described above, Merck had access to that same data, and Merck could have assisted FDA in understanding the data, but instead Merck submitted a prior approval supplement that sought to warn about stress fractures instead of the fractures that FDA had been concerned about, AFFs.

Finally, Merck's acquiescence to FDA's demand to add a label removes any doubt about the current state of the science. *See* J.A. 223-24. Merck, respondents, and FDA all agree that in 2010 there was reasonable evidence of a causal association between Fosamax and atypical femoral fractures. As described above, almost all of the evidence available in 2010, and certainly more than enough of that evidence to support a warning, was available to Merck long before FDA demanded a labeling change.

Merck's position is not, as Merck contends, supported by *Pliva v. Mensing,* 564 U.S. 604 (2011). Pet'r Br. at 28-29. In *Mensing,* the plaintiffs argued that a generic drug manufacturer's failure to warn about a severe neurological disorder associated with use of the drug violated the manufacturer's state law obligation to provide such a warning. 564 U.S. at 609. As the Court pointed out, generic drug manufacturers cannot use the PAS or CBE process that is available to brand name manufacturers. *Id.* at 613. Their labeling "must be the same as" the brand name's labeling. *Id.* As a result, this Court held that it was "impossible" for

the generic drug manufacturer to comply with the state and federal law. *Id.* at 618-19.[7]

The facts of this case, however, do closely track the interactions between the drug manufacturer and the FDA described by the Supreme Court in *Wyeth v. Levine*. Wyeth argued that Levine's failure-to-warn claims were preempted because Wyeth had proposed warning language regarding the risk of intravenous injection of Phenergan, and "FDA rejected Wyeth's proposal." *Wyeth v. Levine*, 555 U.S. at 605 n.1 (Alito, J., dissenting). Although Wyeth's proposed warning 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 opinion). This Court therefore rejected Wyeth's argument because Wyeth had not "attempted to give the kind of warning required by the Vermont jury." *Id.* at 572. The Court held that "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." *Wyeth v. Levine*, 555 U.S. at 571.

Thus, unlike *Pliva*, Merck could have changed its labeling without violating federal law. All Merck had to do was to use the available information to either ask FDA to approve a resubmitted PAS or to use the CBE

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[7] Nor does *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472 (2013), support Merck. In *Bartlett*, the Court rejected plaintiffs' argument that there was no preemption even if the generic manufacturer could have complied with federal and state law by taking its product off of the market. Merck was not faced with this choice because, unlike the generic manufacturers in *Mensing* and *Bartlett,* it had the authority to revise its label.

process to unilaterally change its label without awaiting FDA approval. Nonetheless, Merck did neither.

CONCLUSION

A critical question in this case is whether FDA would have permitted Merck to warn about AFFs prior to the Task Force Report. The Solicitor General and Merck's position that FDA rejected its warning for AFFs is rebutted by the fact that Merck never asked for a warning for AFFs. Instead Merck asked for a warning on stress fractures, and in its complete response letter FDA rejected that request. FDA made it perfectly clear, both in the letter and in a communication that preceded the letter's issuance, that it had not decided on whether to require a warning about AFFs. Thus, under FDA's regulations, Merck could have added a warning about AFFs after giving FDA 30-days' notice of its intent to do so. Since the record shows that FDA had not decided whether a warning about AFFs was appropriate, it would have been consistent with FDA practice to allow Merck to add the warning while the agency was studying the issue.

FDA immediately ordered Merck to add the warning once the Task Force "helped [FDA] understand these fractures" and "clarif[ied] the features of atypical femur fractures." *See supra* p. 19. Merck could have obtained a decision from FDA approving a warning about AFFs in 2009 or earlier if it had offered FDA the analysis that the Task Force provided. Instead Merck chose to obfuscate the true nature of AFFs by focusing its PAS on stress fractures.

A decision preempting respondents' claims here would give pharmaceutical manufacturers an incentive to request permission to add a warning that is not supported by scientific data and then to use FDA's decision rejecting that request as a basis for obtaining preemption of a claim that the manufacturer should have added a related warning that was supported by scientific data. Such a decision would be entirely inconsistent with previous decisions of this Court.

Accordingly, the opinion of the Third Circuit should be affirmed.

RESPECTFULLY submitted.

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