No. 17-290

In the Supreme Court of the United States

MERCK SHARP & DOHME CORP., PETITIONER

v.

DORIS ALBRECHT, ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

BRIAN R. STIMSON
Principal Deputy General Counsel
ELIZABETH H. DICKINSON
Deputy Associate General Counsel
ANNAMARIE KEMPIC
Deputy Chief Counsel, Litigation
KAREN E. SCHIFTER
Senior Counsel
U.S. Department of Health and Human Services
Washington, D.C. 20201

JEFFREY B. WALL
Acting Solicitor General
Counsel of Record
EDWIN S. KNEEDLER
Deputy Solicitor General
ANTHONY A. YANG
Assistant to the Solicitor General
SCOTT R. MCINTOSH
JOSHUA M. SALZMAN
Attorneys
Department of Justice
Washington, D.C. 20530-0001
SupremeCtBriefs@usdoj.gov
(202) 514-2217

QUESTION PRESENTED

Whether a state-law failure-to-warn claim alleging the insufficiency of brand-name drug labeling is preempted by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, when the Food and Drug Administration, after the drug manufacturer provided it with the relevant scientific data, rejected the manufacturer's application to modify its labeling to warn about the risk underlying the tort claim.

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INTEREST OF THE UNITED STATES

This brief is submitted in response to the Court's order inviting the Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be granted.

STATEMENT

1. This case involves a series of tort claims alleging that petitioner's labeling for its Fosamax drug products insufficiently warned of the drugs' risks. Petitioner has argued, *inter alia*, that many of the failure-to-warn claims are preempted because, in 2009, the Food and Drug Administration (FDA) rejected its attempt to strengthen relevant warnings on that labeling. The regulatory scheme for drug labeling sets the stage for that defense.

a. Congress has charged FDA with ensuring that each "drug is safe for use under the conditions prescribed, recommended, or suggested" in its "labeling."

21 U.S.C. 355(d); cf. 21 U.S.C. 352(f) (misbranding). FDA regulations govern the content and format of prescription-drug labeling. See, *e.g.*, 21 C.F.R. 201.56, 201.57; see 21 C.F.R. 201.100(c). Those regulations are intended to organize labeling information to more effectively communicate to healthcare professionals the "information necessary for the safe and effective use of prescription drugs." 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006). Two separate labeling sections now generally required on prescription-drug labeling are relevant here: the Warnings and Precautions section and the Adverse Reactions section. See 21 C.F.R. 201.57(c)(6) and (7).[1]

The Warnings and Precautions section must identify "clinically significant adverse reactions" and certain other safety hazards where "reasonable evidence of a causal association" between the drug and such hazards

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[1] The specific requirements for labeling content and format discussed in the text generally apply to prescription drugs subject to a new drug application (NDA) or efficacy supplement approved on or after June 30, 2001. 21 C.F.R. 201.56(b)(1). The specific labeling requirements for older drug products differ in certain respects. See 21 C.F.R. 201.56(e), 201.80.

This case involves the labeling of three FDA-approved Fosamax products: Fosamax tablets (NDA 20560; approved 1995), Fosamax oral solution (NDA 21575; approved 2003), and Fosamax Plus D tablets (NDA 21762; approved 2005). See C.A. App. A1500; see also FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* 3-12, 6-14 (38th ed. 2018) (listing Fosamax products). Although the newer labeling requirements discussed in this brief did not apply to all of those products at the time relevant here, no party has suggested that the differences between the two sets of labeling requirements are relevant to this case. The government agrees. This brief therefore follows the path taken by the court of appeals, which based its decision on the newer labeling requirements in Section 201.57(c) without discussing Section 201.80. See Pet. App. 7a-9a & nn.6, 9-10, 16, 51a n.130, 63a-64a nn.154, 156.

exists. 21 C.F.R. 201.57(c)(6); see 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (stating that a "'preponderance' of evidence" is not required). FDA adopted that causal standard in part to "prevent overwarning" of potential risks, which, if included in the Warnings and Precautions section, could dilute other "more important warnings" or "deter appropriate use" of the drug. 73 Fed. Reg. at 49,605-49,606. FDA thus reserves this section for only a "discrete set" of hazards serious enough to affect prescribing decisions. FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* 3 (Oct. 2011), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf.[2]

The Adverse Reactions section, by contrast, describes "the overall adverse reaction profile of the drug." 21 C.F.R. 201.57(c)(7). The causal threshold for including an adverse reaction in this section is lower than that for the Warnings and Precautions section: An adverse reaction must be listed if "some basis" exists "to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Ibid.*

b. A brand-name drug "manufacturer bears responsibility for the content of its label[ing] at all times." *Wyeth* v. *Levine*, 555 U.S. 555, 570-571 (2009); see 21 U.S.C. 355(*o*)(4)(I). When new information becomes available about a new risk or a new aspect of a known risk that causes existing labeling to become inadequate,

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[2] The 2011 guidance describes FDA's interpretation of its 2006 labeling regulations, and FDA has informed this Office that the 2011 guidance accurately reflects how FDA treated the Warnings and Precautions section during the period relevant here.

the manufacturer is responsible for pursuing a revision to its labeling. See 21 C.F.R. 201.57(c)(6) (stating that updated warning must be added "as soon as" sufficient causal evidence exists); 21 C.F.R. 201.57(c)(7)(ii)(B) (requiring list of adverse reactions identified in postmarketing experience).[3]

i. After FDA has approved a new drug application (NDA) for a drug, 21 U.S.C. 355(b)(1) and (d), two mechanisms exist for changing a brand-name prescription drug's labeling, both of which require that the manufacturer file a supplemental NDA for FDA approval. First, the sponsor may submit a Changes Being Effected (CBE) supplement for certain labeling changes, which allows the manufacturer immediately to implement its proposed labeling changes upon FDA's receipt of the supplement. 21 C.F.R. 314.70(c)(6) and (iii); see *Wyeth*, 555 U.S. at 571, 573. A CBE supplement may be submitted, *inter alia*, to add or strengthen a warning, precaution, or adverse reaction to reflect "newly acquired information" if "the evidence of a causal association satisfies the [relevant] standard for inclusion in the labeling." 21 C.F.R. 314.70(c)(6)(iii)(A); see 21 C.F.R. 314.3(b) (defining "[n]ewly acquired information"). If FDA later disapproves the supplement, however, it may order the manufacturer to cease distributing the drug with the labeling changes. 21 C.F.R. 314.70(c)(7).

Second, the sponsor may submit a Prior Approval Supplement (PAS) to propose labeling changes, under which FDA approval is required before the changes are made. 21 C.F.R. 314.70(b)(2)(v)(A) and (3). A PAS

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[3] Because a generic drug's labeling generally must track that of its reference listed drug, generic-drug manufacturers cannot independently change such labeling. See, *e.g.*, *Mutual Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 486, 488 (2013).

"must be submitted" for certain types of changes that "include, but are not limited to," certain labeling changes other than those described in Section 314.70(c)(6)(iii) for CBE supplements. 21 C.F.R. 314.70(b)(1), (2), and (v)(A). Historically, FDA has also accepted PAS applications instead of CBE supplements, as occurred in this case, particularly where significant questions exist on whether to revise or how to modify existing drug labeling.[4]

ii. "All procedures and actions that apply to an application" submitted to FDA generally apply "to supplements." 21 C.F.R. 314.71(b) and (c). FDA has accordingly confirmed to this Office that it follows many of the general principles applicable to its review of an NDA when undertaking the more limited task of reviewing supplements that propose safety-related labeling changes. More specifically, FDA communicates with the applicant about "scientific, medical, and procedural issues that arise" in the course of its review. 21 C.F.R. 314.102(a). The "[d]evelopment of final labeling" generally is then "an iterative process between the applicant and FDA" involving a series of communications.[5] If FDA reviewers identify "easily correctable deficiencies" in a supplement,

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[4] Cf. FDA, *Guidance for Industry: Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* 7 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

[5] See Center for Drug Evaluation & Research, FDA, *CDER 21st Century Review Process: Desk Reference Guide* 37 (2014), https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf; see also FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* 21 (Apr. 2005), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079748.pdf (addressing "communication between the FDA and applicants" during "labeling discussions").

they will "make every reasonable effort to communicate [them] promptly to applicants." 21 C.F.R. 314.102(b). And if only "editorial or similar minor deficiencies in the [proposed] labeling" exist, FDA may approve the supplement on the condition that the applicant makes appropriate corrections and submits a copy of the final labeling before marketing the drug with that labeling. 21 C.F.R. 314.105(b).

FDA will reject a supplement, however, if the proposed labeling change is false or misleading or if it does "not comply with the requirements for labels and labeling in [21 C.F.R. P]art 201." 21 C.F.R. 314.125(b)(6) and (8). In such circumstances, FDA will send the applicant a "complete response letter." 21 C.F.R. 314.110(a). A complete response letter reflects FDA's "complete review of the data submitted" and "will describe all of the specific deficiencies that the agency has identified." 21 C.F.R. 314.110(a)(1) and (2).

2. a. Petitioner is the manufacturer of Fosamax, a brand-name drug that FDA approved in tablet form in 1995 for the treatment of osteoporosis in postmenopausal women. Pet. App. 5a, 12a; see p. 2 n.1, *supra*. Evidence later began to emerge suggesting a connection between Fosamax and an increased risk of an unusual type of thigh-bone fracture known as an "atypical femoral fracture[]," which occurs with no or minimal external trauma and results in a complete fracture of the femur. Pet. App. 6a, 13a-14a. Petitioner kept FDA informed of those studies. *Id.* at 13a.

In June 2008, FDA informed petitioner that it was aware of reports regarding the occurrence of fractures in patients using bisphosphonates like Fosamax. Pet. App. 14a. FDA stated that it was "concerned about this developing safety signal" and asked petitioner to submit

any information it had on the issue. *Ibid.* (citation omitted). Petitioner promptly complied. *Ibid.*

b. In September 2008, petitioner submitted three Prior Approval Supplements for its three Fosamax products that proposed changing the relevant labeling to address atypical femoral fractures in two respects. Pet. App. 14a-15a; see p. 2 n.1, *supra*.[6] First, in the Adverse Reactions section, petitioner proposed adding a reference to "low-energy femoral shaft fracture." Pet. App. 16a (quoting C.A. App. A1383). Second, in the Warnings and Precautions section, petitioner proposed adding a new subsection with an identical title: "Low-Energy Femoral Shaft Fracture." *Id.* at 15a (quoting C.A. App. A1371) (emphasis omitted). That subsection stated that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." C.A. App. A1371. The proposed warning added that "[s]ome" of those fractures were "stress fractures," and the remainder of petitioner's proposed text repeatedly referenced stress fractures. *Ibid.*

Petitioner supported its applications with evidence regarding femoral fractures in Fosamax users. Pet. App. 16a. The applications stated, *inter alia*, that petitioner's use of the term "stress fracture" in connection with reports of "low-energy subtrochanteric/mid femoral shaft fractures" referred to an "insufficiency fracture" that occurs with no "identifiable external traumatic event." C.A. App. A2751-A2752; see *id.* at

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[6] Relevant portions of one of the PAS applications are available at C.A. App. A2697-A2928. See *id.* at A1349-A1388 (duplicative). FDA has confirmed to this Office that petitioner proposed the same relevant labeling language for each of its three Fosamax products.

A2754.[7] The treatment data in the applications indicated that 91% of the fractures resulted in surgical intervention and the other 9% involved patients who sustained only "incomplete stress fractures." *Id.* at A2755.

In May 2009, FDA issued a Complete Response Letter informing petitioner that FDA could not "approve the[] applications in their present form." Pet. App. 18a (quoting C.A. App. A1500). FDA stated that it "agree[d] that atypical and subtrochanteric fractures should be added" to the Adverse Reactions labeling section. C.A. App. A1500. FDA therefore "recommend[ed]" that petitioner modify its proposed text for that section to read "low energy femoral shaft and subtrochanteric fractures." *Id.* at A1501. With respect to petitioner's Warnings and Precautions proposal, however, FDA determined that the "justification for the proposed [Warnings and Precautions] section language is inadequate." *Id.* at A1500. The letter also stated that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature" and that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." *Id.* at A1500-A1501.

In June 2009, petitioner updated the Adverse Reactions section of its Fosamax labeling using FDA's recommended text. C.A. App. A1141, A1143. Petitioner

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[7] An "insufficiency f[racture]"—which can be associated with "osteoporosis"—is "a stress fracture that occurs during normal stress on a bone of abnormally decreased density"; it is thus different from the type of "stress f[racture]" experienced by athletes (a fatigue fracture) "caused by unusual or repeated stress on a bone." *Dorland's Illustrated Medical Dictionary* 710-711 (29th ed. 2000).

then withdrew its three pending PASs and submitted new CBE supplements for that labeling change (which FDA later approved) as the "quickest route to update" its labeling. 11-cv-5304 Doc. 26, Ex. 12, at 6279, 64,461.[8]

c. Nearly a year after its Complete Response Letter, and after reviewing additional data submitted by petitioner and other manufacturers, FDA issued a Safety Announcement in March 2010 stating that the data at that time had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures," but that FDA was working with an outside expert task force to gather additional information. C.A. App. A1508; see Pet. App. 19a.

In September 2010, the task force completed its report, which identified an apparent association between long-term bisphosphonate use and certain atypical femoral fractures. Pet. App. 20a. In October 2010, FDA announced that it was requiring bisphosphonate manufacturers to modify their labeling to include information regarding the risk of such fractures in, *inter alia*, the Warnings and Precautions section. C.A. App. A1118. Shortly thereafter, FDA approved that labeling change for Fosamax. Pet. App. 21a-23a. Before approving that labeling, FDA eliminated references to "stress fractures" from petitioner's proposal because, FDA concluded, the term would suggest to most practitioners "a minor fracture" that "would contradict the seriousness

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[8] See FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/020560s051s055s057,021575s012s016s018ltr.pdf (NDA 20560/S-057 and 21575/S-018); FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021762s005s009sS010ltr.pdf (NDA 21762/S-010).

of the atypical femoral fractures" at issue. *Id.* at 22a-23a (citation omitted).

3. Over 1000 plaintiffs subsequently filed separate state-law tort actions against petitioner, alleging that they had sustained atypical femoral fractures caused by taking Fosamax. Pet. App. 4a, 23a. Although plaintiffs asserted an array of tort theories, they generally alleged that petitioner had failed to provide adequate warnings on its Fosamax labeling. *Id.* at 4a, 24a. The cases were consolidated for pretrial proceedings as a multidistrict litigation (MDL). *Id.* at 23a.

One bellwether case within the MDL was selected for trial on its failure-to-warn claim. Pet. App. 24a-25a & n.64. Petitioner moved for summary judgment on preemption grounds, but the district court did not immediately rule on the motion. *Id.* at 163a. After a jury rendered a verdict for petitioner on case-specific grounds, the court rendered a post-trial decision holding that the bellwether plaintiffs' failure-to-warn claim was preempted. *Id.* at 25a-26a, 153a-174a.

The district court subsequently applied that holding to the other MDL cases in which the plaintiff was injured before September 14, 2010—the date of the FDA task force report—and granted judgment to petitioner in those cases. Pet. App. 152a; see *id.* at 113a-152a.

4. The court of appeals vacated and remanded. Pet. App. 1a-74a.

The court of appeals concluded that its impossibility-preemption analysis was controlled by this Court's decision in *Wyeth* v. *Levine, supra*, which the court viewed as teaching that a drug-focused failure-to-warn claim is preempted "where there is 'clear evidence that the FDA would not have approved a change' to the label," Pet. App. 32a-33a (quoting *Wyeth*, 555 U.S. at 571). See *id.*

at 28a-55a. The court concluded that *Wyeth*'s "clear evidence" discussion "announce[d] a standard of proof" that is "synonymous with 'clear and convincing evidence'" and required proof showing it "is highly probable that the FDA would not have approved a change to the drug's label." *Id.* at 35a, 37a; see *id.* at 33a-37a. The court further concluded that the relevant preemption determination—which involves "predict[ing] how the FDA would have reacted in a hypothetical scenario" involving a new proposal to strengthen labeling warnings, *id.* at 51a-52a—is a factual determination for a jury, not a legal one for a court. *Id.* at 38a-55a.

Applying those principles, the court of appeals held that summary judgment should not have been granted to petitioner. Pet. App. 55a-74a. As relevant here, the court determined that a "reasonable jury" could conclude that petitioner could have revised the Warnings and Precautions section of its labeling before September 2010. *Id.* at 56a-57a, 67a. A jury, the court reasoned, could find that FDA's 2009 decision to reject petitioner's proposed revision to that section was not based on FDA's determination that the evidence at the time was insufficient to indicate that Fosamax caused atypical femoral fractures, but rather was based on FDA's dissatisfaction with the proposal's use of the term "stress fractures," which medical practitioners might misunderstand to refer to fractures less serious than the femoral fractures in question, *id.* at 64a-66a. See *id.* at 59a-68a.[9]

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[9] The court of appeals also concluded that the district court erred in granting summary judgment on claims based on the Adverse Reactions section of Foxamax's labeling before its 2009 revision, Pet. App. 69a-73a, and on non-failure-to-warn claims, *id.* at 74a.

DISCUSSION

The court of appeals erred in holding that a jury must determine whether FDA's May 2009 decision—which declined to approve petitioner's proposal to revise Fosamax's Warnings and Precautions section to warn against "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," C.A. App. A2720—preempted respondents' state-law failure-to-warn claims arising from that same type of injury. Where, as here, FDA renders a decision declining to approve a drug-labeling change, the interpretation of that administrative decision and its significance for a failure-to-warn claim are legal questions for a court to resolve, not factual questions for a jury. Moreover, because FDA's decision here prevented petitioner from modifying the relevant labeling before late 2010, the court of appeals erred in rejecting petitioner's impossibility-preemption defense.

In the view of the United States, this Court should grant review. The underlying issue—whether the meaning and effect of an FDA labeling decision present a question of law for courts to resolve or a question of fact for lay juries to determine—is significant. The petition cleanly presents that issue in a context in which hundreds of separate cases asserting similar failure-to-warn claims turn on its proper resolution. No circuit conflict yet exists, however, and further percolation in the courts of appeals could potentially refine the issue for review. Although the question is close, the government concludes that, on balance, review is warranted at this time.

I. THE COURT OF APPEALS ERRED IN REJECTING PETITIONER'S PREEMPTION DEFENSE

A. The Meaning And Effect Of FDA's May 2009 Decision Present A Legal Question That A Court Must Resolve

The court of appeals held that the relevant task in resolving petitioner's preemption defense "is to predict how the FDA would have reacted in a hypothetical scenario" involving "a different label amendment than the one it actually rejected in [its] May 2009 letter." Pet. App. 51a-52a. The court thus concluded that the proper focus is not the "legal effect" of FDA's May 2009 decision but what the agency's decision letter "suggests about the FDA's likely response to a differently worded proposal." *Id.* at 52a. That is incorrect. The proper focus here is on whether FDA's May 2009 decision embodied a determination by FDA that insufficient causal evidence existed at the time to warrant strengthening Fosamax's Warnings and Precautions section to address atypical femoral fractures. That is a question of law for a court to resolve, not a question of fact for a jury.

1. A federal agency's written decision on a regulatory application is a legal document: an agency action that embodies the agency's exercise of legal authority to adjudicate that application. Cf. 5 U.S.C. 551(6) and (7) (defining agency adjudication). The meaning and effect of such agency action is a legal question within the exclusive province of a court.

When Congress enacted the Administrative Procedure Act (APA), 5 U.S.C. 551 *et seq.*, 701 *et seq.*, it specified that a "reviewing court shall * * * determine the meaning or applicability of the terms of an agency action." 5 U.S.C. 706. That provision reflects the longstanding view that the "application" of "any agency action" and "questions respecting the * * * terms of

[such] action" are "questions of law" and therefore matters for "courts * * * to decide." H.R. Rep. No. 1980, 79th Cong., 2d Sess. 44 (1946); see U.S. Dep't of Justice, *Attorney General's Manual on the Administrative Procedure Act* 108 (1947) (APA's review provision "restates the present law").

The legal nature of that inquiry is consistent with this Court's precedent addressing the meaning and effect of a prior judicial adjudication. When issues adjudicated in prior litigation are relevant to factfinding in a subsequent civil action, this Court has held that the question of "[w]hat issues were decided [in that prior] litigation is * * * a question of law" that the trial court must itself decide by examining relevant materials from the prior case. *Emich Motors Corp.* v. *General Motors Corp.*, 340 U.S. 558, 571-572 (1951). That holds true even where a jury must consider "the scope and effect of the former judgment on the case at trial"; in such circumstances, the trial court must first determine the prior adjudication's scope and effect before "instruct-[ing] the jury" on its legal determination. *Ibid.* Just as the scope of such a prior judicial adjudication is a question of law for a court to decide, so too is the scope of a federal agency adjudication like that at issue here.

No sound reason exists for treating the meaning and effect of an FDA administrative determination any differently. Judges, rather than lay juries, are best suited to evaluate the scope of an agency's legal determination in light of the relevant statutory and regulatory context. Moreover, framing the decision as a question of law to be decided by judges familiar with principles of administrative law will foster the type of uniformity appropriate when determining the scope and effect of federal agency action. See *Markman* v. *Westview Instruments,*

Inc., 517 U.S. 370, 390-391 (1996). Whether the agency action is a notice-and-comment regulation or something less formal like the adjudicatory decision at issue here, the meaning of such agency action is a legal question that a court should decide. Cf. *Perez* v. *Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1208 n.4 (2015) ("[I]t is the court that ultimately decides wh[at] a given regulation means.").

In this case, as explained below, the basis for FDA's 2009 Fosamax labeling decision is properly determined as a matter of law from FDA's Complete Response Letter, read in the context of petitioner's underlying labeling supplement and the surrounding regulatory framework and related FDA actions. Even if disputed subsidiary factual questions were relevant to determining the meaning and effect of the agency's 2009 decision, the ultimate inquiry would remain a legal one. This Court in *Markman* confronted analogous circumstances when it held that "the construction of a patent" is a "purely legal" issue "exclusively within the province of the court." 517 U.S. at 372, 391. The Court reasoned that "judges, not juries, are the better suited" for discerning the meaning of patent terms, even though factual questions involving "credibility determinations" are sometimes "subsumed" within the relevant analysis. *Id.* at 388-389; see *Teva Pharm. USA, Inc.* v. *Sandoz, Inc.*, 135 S. Ct. 831, 838 (2015) (explaining that the "ultimate issue of the proper construction of a [patent] claim [is] treated as a question of law," even though "subsidiary factfinding is sometimes necessary"). The same rationale applies here. To the extent extrinsic evidence may sometimes be relevant to determine the meaning and effect of FDA's agency action in litigation

between private parties (which typically will lack compilation of an official administrative record), the court's evaluation of such subsidiary facts does not alter the ultimate legal character of the inquiry.

2. The court of appeals concluded that, in order to sustain petitioner's preemption defense, this Court's decision in *Wyeth* v. *Levine*, 555 U.S. 555 (2009), required that petitioner provide "clear evidence" that could establish to a jury that FDA "would [have] reject[ed] [the] plaintiff's proposed warning" for Fosamax if petitioner had proposed that warning to FDA. Pet. App. 33a, 54a. In addressing that purported "hypothetical scenario," the court of appeals determined that a jury could reasonably conclude that "FDA rejected [petitioner's] proposed warning about femoral fractures in 2009 not because" FDA deemed the "causal link between Fosamax and fractures" to be insufficient, but because FDA was dissatisfied with petitioner's proposed text. *Id.* at 51a, 64a-65a. Nothing is "hypothetical" about FDA's *actual* 2009 decision in this case, and nothing in *Wyeth* addresses how courts should determine the meaning and effect of such (actual) agency action.

In *Wyeth*, this Court determined that a state-law failure-to-warn claim involving a brand-name drug was not foreclosed by the doctrine of impossibility preemption, because the drug manufacturer had a duty to ensure the adequacy of its own labeling and could have invoked FDA's CBE regulation to update its labeling promptly to provide additional warnings in response to newly acquired information. 555 U.S. at 570-573. The Court recognized that "FDA retains authority to reject [a manufacturer's unilateral] labeling changes made pursuant to the CBE regulation," *id.* at 571, but it explained that Wyeth did "not argue" that any actual FDA

decision had "prohibited" it from strengthening its labeling, *id.* at 572.

The Court instead viewed Wyeth as arguing that FDA had "intended to prohibit it" from changing the label when FDA originally approved the relevant drug, a contention that the courts below had rejected. 555 U.S. at 572 & n.5. Thus, without any actual agency decision at hand, this Court stated that it would not conclude that it was impossible for Wyeth to comply with both federal and state requirements "absent clear evidence that the FDA *would not have approved* a change to [the] label[ing]" in question. *Id.* at 571 (emphasis added). In other words, the Court reasoned that Wyeth needed to make a clear showing that "FDA would have rescinded any change in the label" to establish that it would have been impossible to make such a change. *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 624 n.8 (2011). This Court then rejected Wyeth's impossibility defense because the manufacturer, which did "not argue" that it had provided FDA with an analysis of the "specific dangers" in question, failed to show that "FDA would have prevented it from adding a stronger warning." 555 U.S. at 572-573.

Because *Wyeth* discussed the question whether FDA would have rejected a CBE labeling change *if* the manufacturer in that case had unilaterally made such a change to strengthen its labeling, *Wyeth* did not resolve how to determine the meaning and effect of an actual FDA labeling-supplement decision. For that reason, the court of appeals erred in transplanting *Wyeth*'s discussion about a hypothetical regulatory scenario to support a requirement for "clear evidence" about the scope and effect of the actual agency labeling decision in this

case. This Court has long cautioned that it is "often misleading" to transplant "[g]eneral expressions" from one opinion "to other facts" because every opinion must be "read in the light of the facts of the case under discussion." *Armour & Co.* v. *Wantock*, 323 U.S. 126, 133 (1944); see *Landgraf* v. *USI Film Prods.*, 511 U.S. 244, 265 (1994) (quoting *Cohens* v. *Virginia*, 19 U.S. (6 Wheat.) 264, 399 (1821) (Marshall, C.J.)).

3. This case does not present circumstances in which there is no actual FDA labeling decision to interpret—for instance, because the manufacturer did not submit a labeling supplement. In such circumstances, *Wyeth*'s use of the phrase "clear evidence" could arguably be read to suggest that determining what FDA would have done with respect to such a supplement presents a question of fact for the jury to decide. See Pet. App. 33a-55a. But *Wyeth* did not squarely address or definitively resolve that issue with the phrase "clear evidence." See *id.* at 28a, 33a-35a (noting that *Wyeth*'s discussion was "cryptic"). This Court in another context, for example, has used the even more specific phrase "clear and convincing evidence" not in its "strict evidentiary sense" but merely as a "useful reminder" that a general presumption concerning a *legal interpretation* should control if substantial doubt exists about "congressional intent." *Block* v. *Community Nutrition Inst.*, 467 U.S. 340, 350-351 (1984). By analogy here, *Wyeth* may simply reflect that a persuasive legal showing is necessary to establish preemption when no relevant FDA decision exists.

Wyeth therefore may be understood as consistent with the view that, to establish impossibility preemption, a name-brand drug manufacturer cannot rely on

speculation or merely plausible interpretations of ambiguous features of FDA's regulatory framework and practices. Rather, on this understanding of *Wyeth*, the manufacturer must demonstrate, on the basis of historical facts concerning its own conduct and available studies and data at the time, that the agency reasonably would have concluded that a labeling change was not warranted under the relevant statutory and regulatory framework. This case does not require the Court to consider that scenario, however, because the relevant question here is how to interpret FDA's actual labeling decision in this case.

B. FDA's May 2009 Decision Rejected A Change To Fosamax's Warnings And Precautions Because The Data At That Time Was Insufficient To Justify A Change

FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures was based on the agency's determination that the data was then insufficient to justify such a warning. That conclusion flows directly from the terms of the agency's May 2009 Complete Response Letter, the relevant regulatory context, and the agency's subsequent actions. Given FDA's determination, respondents' claim that petitioner should have updated its Warnings and Precautions labeling at that time is preempted.[10]

FDA's Complete Response Letter (C.A. App. A1500-A1501) shows that FDA determined that the existing data for atypical femoral fractures was sufficient to update Fosamax's Adverse Reactions section, but not its

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[10] The question presented is based on the premise that petitioner provided FDA with "the relevant scientific data," Pet. i, and respondents' brief in opposition does not appear to contend otherwise.

Warnings and Precautions section. FDA determined that "atypical and subtrochanteric fractures should be added" as adverse reactions, *id.* at A1500, reflecting that FDA found "some basis to believe there [wa]s a causal relationship between the drug and the occurrence of th[at] adverse event." 21 C.F.R. 201.57(c)(7). Petitioner's proposed Warnings and Precautions revision was based on the same risk. Among other things, petitioner's proposed title ("Low-Energy Femoral Shaft Fracture") for its proposed subsection in Warnings and Precautions was identical (with only differing capitalization) to its proposed text for the Adverse Reactions section. Pet. App. 15a-16a (citation and emphasis omitted). The proposed warning also addressed the same type of adverse reaction that FDA agreed should be added to Fosamax's labeling. See *id.* at 15a ("[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft") (citation omitted).

Under the governing regulations, however, such an adverse reaction is to be elevated to the Warnings and Precautions section only if "reasonable evidence of a causal association with [the] drug" exists. 21 C.F.R. 201.57(c)(6)(i). Here, FDA rejected petitioner's addition because the "*justification* for the proposed [Warnings and Precautions] section language [wa]s inadequate." C.A. App. A1500 (emphasis added). Petitioner had also proposed stating that "[s]ome" of the reported fractures were "insufficiency" "stress fractures," *id.* at A1371; see pp. 7-8 & n.7, *supra*, but FDA determined that such fractures "may not be clearly related to the atypical subtrochanteric fractures * * * *reported in the literature*," and the associated discussion of stress-fracture risk factors was likewise "not adequately *supported by the available literature and post-marketing*

adverse event reporting." C.A. App. A1500-A1501 (emphases added). FDA's decision thus was based on the lack of adequate data to support a warning.

The court of appeals focused instead on the possibility that "FDA [might have] rejected [petitioner's] proposed warning" because of the warning's use of the term "stress fractures." Pet. App. 64a-65a. But a Complete Response Letter reflects "FDA's complete review of the *data* submitted"; the letter need not address any "proposed product labeling" if FDA determines that the "data submitted are inadequate." 21 C.F.R 314.110(a)(2) and (3) (emphasis added). If a warning is warranted, FDA will attempt promptly to identify easily correctable deficiencies in the proposed text and will then develop final labeling text with the manufacturer in an iterative process. See pp. 5-6, *supra*. The May 2009 letter thus embodies FDA's "recommend[ation]" that petitioner modify its proposed Adverse Reactions text with language (shown here in italics) that FDA itself proposed: "low energy femoral shaft *and subtrochanteric* fractures." C.A. App. A1501 (emphasis added); cf. Pet. App. 16a (petitioner's proposal). And in late 2010, when FDA concluded that the Warnings and Precautions section should also be revised, FDA itself edited petitioner's language to remove stress-fracture references it deemed insufficiently clear. Pet. App. 22a-23a. No sound basis thus exists for concluding that FDA determined in May 2009 that the data was sufficient to warrant a warning but that it rejected petitioner's proposal because of petitioner's proposed text.

FDA's own regulations require that the Warnings and Precautions section "must be revised" to add such a clinically significant hazard "*as soon as*" sufficient

causal evidence exists. 21 C.F.R. 201.57(c)(6)(i) (emphasis added). If FDA had "believe[d]" in May 2009 that the "new safety information" that petitioner had submitted "should [have] be[en] included in [Fosamax's] labeling," Section 355(*o*)(4) would have required that FDA "promptly notify" petitioner, 21 U.S.C. 355(*o*)(4)(A), and engage in expedited discussions to revise the labeling, 21 U.S.C. 355(*o*)(4)(B)-(D). In 2009, however, FDA concluded in its Complete Response Letter that the justification for an enhanced warning was insufficient. Indeed, nearly a year later, FDA announced—after reviewing further data—that it had yet to find any "clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Pet. App. 19a (citation omitted). It was only in October 2010—after an external task force had completed its report on the issue—that FDA came to "believe that the information" about atypical femoral fractures should be added to the Warnings and Precautions section and therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax and other bisphosphonates. See C.A. App. A1515-A1516.

II. THE COURT OF APPEALS' DECISION WARRANTS REVIEW

Although the question is close, in the view of the United States, this Court should grant certiorari. The underlying issue in this preemption case is a significant one: whether the meaning and effect of an FDA labeling decision is a question of law for courts to resolve or a question of fact for lay juries to determine. The petition cleanly presents that issue in an MDL context in which hundreds of separate cases asserting similar failure-to-

warn claims turn on its proper resolution. The hundreds of trials that could ensue are unlikely to clarify the issue for review.

To be sure, petitioner correctly does not contend that the court of appeals' decision here has yet given rise to a circuit conflict. Cf. Pet. 14. It is also unclear whether the decision below will influence other courts addressing similar preemption defenses. No court of appeals, for instance, has focused on the principle that the interpretation of federal agency action is traditionally a legal question for courts to decide. Allowing the issue to "mature through full consideration by the courts of appeals" could thus potentially "simplif[y the Court's] task" by refining the issue for its review. *E.I. du Pont de Nemours & Co.* v. *Train*, 430 U.S. 112, 135 n.26 (1977).

On balance, however, the government concludes that review is warranted at this time. The legal question, although narrow in the context of this case involving an FDA decision rejecting a proposed labeling change, is important and cleanly presented. Its practical implications are starkly illustrated by the volume of tort claims asserted against petitioner in this case. And the Court's consideration of the proper method for resolving the preemption issue in this case may inform the proper analytical framework for resolving FDA preemption issues in light of *Wyeth* more generally.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

BRIAN R. STIMSON[**]
Principal Deputy General Counsel
ELIZABETH H. DICKINSON
Deputy Associate General Counsel
ANNAMARIE KEMPIC
Deputy Chief Counsel, Litigation
KAREN E. SCHIFTER
Senior Counsel
U.S. Department of Health and Human Services

JEFFREY B. WALL[*]
Acting Solicitor General
EDWIN S. KNEEDLER
Deputy Solicitor General
ANTHONY A. YANG
Assistant to the Solicitor General
SCOTT R. MCINTOSH
JOSHUA M. SALZMAN
Attorneys

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[*] Solicitor General Noel J. Francisco is recused from this matter.

[**] General Counsel Robert P. Charrow is recused from this matter.