852 F.3d 268
United States Court of Appeals,
Third Circuit.

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION

Nos. 14-1900 et al.*
|
Argued June 30, 2016
|
(Opinion Filed: March 22, 2017)

* This opinion applies to all appeals listed in Appendix A, attached.

Synopsis
Background: Consumers brought separate products liability actions against drug manufacturer, asserting state-law failure-to-warn claims alleging that manufacturer failed to add an adequate warning of risk of atypical femur fractures to FDA-approved label for its osteoporosis drug. Actions were consolidated for pretrial administration in a multidistrict litigation. The United States District Court for the District of New Jersey, Nos. 3:08-cv-00008-FLW et al., MDL No. 2243, Joel A. Pisano, J., 2014 WL 1266994, entered summary judgment for manufacturer, and consumers appealed.

Holdings: The Court of Appeals, Fuentes, Circuit Judge, held that:

[1] for a manufacturer to establish an impossibility preemption defense, factfinder must conclude that it was highly probable that Food and Drug Administration (FDA) would not have approved a label change;

[2] whether FDA would have rejected a proposed drug label change is a question of fact for jury; and

[3] fact issue precluded summary judgment on manufacturer's impossibility preemption defense.

Vacated and remanded.

***270** On Appeal from the United States District Court for the District of New Jersey (D.C. Nos. 3:08-cv-00008-FLW *et al*., MDL No. 2243) District Judge: Honorable Joel A. Pisano

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Before: FUENTES, CHAGARES, and RESTREPO, Circuit Judges

OPINION OF THE COURT

FUENTES, Circuit Judge.

Beginning in 2010, hundreds of plaintiffs filed personal-injury suits against the drug manufacturer Merck Sharp & Dohme, alleging that the osteoporosis drug Fosamax

caused them to suffer serious thigh bone fractures. Each Plaintiff brought a state-law tort claim alleging that Merck failed to add an adequate warning of the risk of thigh fractures to Fosamax's FDA-approved drug label. Many Plaintiffs also brought a variety of additional claims including defective design, negligence, and breach of warranty.

Plaintiffs' suits were consolidated for pretrial administration in a multi-district litigation in the District of New Jersey. Following discovery and a bellwether trial, the District Court granted Merck's motion for summary judgment and dismissed all of Plaintiffs' claims on the ground that they were preempted by federal law. The District Court based its ruling on the Supreme Court's decision in *Wyeth v. Levine*,[1] which holds that state-law failure-to-warn claims are preempted when there is "clear evidence" that the FDA would not have approved the warning that a plaintiff claims was necessary.

[1] 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009).

We will vacate and remand. Preemption is an affirmative defense, and Merck has not carried its burden to prove that it is entitled to that defense as a matter of law. The *Wyeth* "clear evidence" standard is demanding and fact-sensitive. It requires the factfinder to predict a highly probable outcome in a counterfactual world and, therefore, requires a court sitting in summary judgment to anticipate both the range of conclusions that a reasonable juror might reach and the certainty with which the juror would reach them. Here, Plaintiffs have produced sufficient evidence for a reasonable jury to conclude that the FDA would have approved a properly-worded warning about the risk of thigh fractures—or at the very least, to conclude that the odds of FDA rejection were less than highly probable. Under *Wyeth* and Rule 56, that is enough for Plaintiffs to defeat summary judgment and proceed to trial.

I. BACKGROUND

A. Fosamax and Atypical Femoral Fractures

Fosamax is a drug manufactured by Merck that belongs to a class of drugs known as bisphosphonates. The Food and Drug Administration ("FDA") approved Fosamax in the 1990s for the treatment and prevention of osteoporosis in postmenopausal women.

Fosamax treats osteoporosis by correcting an imbalance in the so-called "bone remodeling" process. Throughout a person's life, bones are continuously broken down through a process called resorption and then reformed by the creation of new ***272** bone cells. In postmenopausal women, the rate of bone resorption exceeds that of bone formation, thereby causing bone loss. If bone loss continues unchecked, a person may develop osteoporosis, "a disease characterized by low bone mass and deterioration of bone structure that causes bone fragility and increases the risk of fracture."[2] Bisphosphonates like Fosamax slow the resorption process, restoring the balance between resorption and formation and reducing the risk of osteoporotic fracture.

[2] U.S. Dep't of Health & Human Servs., *Bone Health and Osteoporosis: A Report of the Surgeon General* 41 (2004).

Plaintiffs claim, however, that Fosamax can actually increase the risk of certain bone fractures. They allege that by slowing resorption, bisphosphonates inhibit bone repair. According to Plaintiffs, bones frequently develop so-called "microcracks," which are ordinarily repaired through the resorption process. An accumulation of microcracks can lead to incomplete bone fractures called "stress fractures." The standalone term "stress fracture" typically connotes a fracture resulting from excessive loading of a normal bone, and is commonly seen in physically active individuals. A so-called "insufficiency stress fracture," by contrast, is a fracture caused by normal loading of poor-quality bone. Plaintiffs claim that while stress fractures typically heal on their own, "some Fosamax users who develop insufficiency fractures have reduced bone toughness, and Fosamax prevents the normal repair of the fracture."[3] According to Plaintiffs, these patients may then go on to develop what are known as "atypical femoral fractures": severe, non-traumatic, low-energy complete fractures of the femur.

[3] Pls. Br. 15 (citing A 884.)

Plaintiffs in this case are all Fosamax users who suffered atypical femoral fractures. They allege, among other

things, that (1) Fosamax caused these atypical fractures by slowing the resorption process and allowing microcracks to accumulate, and (2) Merck was aware of the risk of such fractures but acted unlawfully by failing to warn doctors and patients of those dangers. They claim that Merck should have included a warning about atypical femoral fractures in the federally-mandated drug warnings that accompany prescription drugs. The interplay, and potential collision, between state-law warning duties and federal regulatory requirements is the subject of this appeal.

B. Regulatory Framework

The Food, Drug, and Cosmetic Act ("FDCA")[4] regulates the marketing and sale of prescription drugs in the United States. Under the FDCA, a manufacturer must obtain approval from the United States Food and Drug Administration ("FDA") before marketing a new drug.[5] As part of a new drug application, the manufacturer must submit a proposed package insert, commonly called the "drug label," that sets out the drug's medical uses ("indications") and health risks.[6] "To obtain FDA approval, drug companies generally must submit evidence from clinical trials and other testing that evaluate the drug's risks and benefits and demonstrate that it is safe and effective for all of the indications 'prescribed, recommended, or suggested' on the drug's label."[7] The FDA's ***273** approval of a new drug application is conditioned on its approval of the exact text of the drug label.[8]

4 21 U.S.C. § 301 *et seq*.

5 *Id*. § 355(a).

6 21 C.F.R. § 201.57(a); 21 U.S.C. § 355(b)(1)(F).

7 *In re Schering Plough Corp. Intron/Temodar Consumer Class Action*, 678 F.3d 235, 239 (3d Cir. 2012) (quoting 21 U.S.C. § 355(d)).

8 21 C.F.R. § 314.105(b), (c).

Drug labels includes two sections relevant to this litigation: a "Warnings and Precautions" section and an "Adverse Reactions" section. The Warnings and Precautions section must describe "clinically significant adverse reactions," including any that are "serious even if infrequent."[9] The Adverse Reactions section requires a description of "the overall adverse reaction profile of the drug based on the entire safety database," including a list of all "undesirable effect[s], reasonably associated with use of a drug."[10]

9 *Id*. § 201.57(c)(6)(i).

10 *Id*. § 201.57(c)(7).

After a drug is approved, the FDA retains the authority to approve or require amendments to the drug's label.[11] The fundamental premise of the federal drug labeling scheme, however, is that "manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."[12] The manufacturer is charged not only "with crafting an adequate label" as an initial matter, but also "with ensuring that its warnings remain adequate as long as the drug is on the market."[13]

11 21 U.S.C. § 355(o)(4); 21; C.F.R. § 314.93; *see also Wyeth*, 555 U.S. at 567, 129 S.Ct. 1187 (observing that the 2007 FDCA amendments "granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval").

12 *Wyeth*, 555 U.S. at 579, 129 S.Ct. 1187; *see also* 21 U.S.C. § 355(o)(4)(I) ("Rule of construction" clarifying that the 2007 amendments to the FDCA "shall not be construed to affect the responsibility of the responsible person ... to maintain its label in accordance with existing requirements").

13 *Wyeth*, 555 U.S. at 571, 129 S.Ct. 1187.

A manufacturer can fulfill its responsibility to revise the warnings on a drug label in two ways.

First, the "Changes Being Effected" ("CBE") regulation permits a manufacturer to unilaterally change a drug label to reflect "newly acquired information," subject to later FDA review and approval.[14] Under the CBE regulation, the manufacturer may, upon filing a supplemental application with the FDA, change a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction"; it need not wait for FDA approval.[15] To add a warning to the Warnings and Precautions section through a CBE submission, "there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence."[16] Thus, a manufacturer can amend the label to address potential adverse effects even if the evidence for a causal connection would "not also support a higher evidentiary standard, such as a finding that there is a 'preponderance' of evidence that a product actually causes a particular kind of adverse event."[17]

14 21 C.F.R. § 314.70(c)(6)(iii); *see also Wyeth*, 555 U.S. at 568, 129 S.Ct. 1187 (discussing CBE amendment process).

15 *Id*. § 314.70(c)(6)(iii)(A).

16 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (FDA notice regarding final amendment to CBE regulation); *see also* 21 C.F.R. 201.57(c)(6)(iii) (Warnings and Precautions 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.").

17 73 Fed. Reg. at 49,604.

***274** For purposes of the CBE regulation, "newly acquired information" includes "new analyses of previously submitted data."[18] This definition "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments."[19] Thus, if a manufacturer were to "determine[ ] that existing warnings were insufficient based on ... a new analysis of previously submitted data, [it] could still submit a CBE based on its new analysis of the previous data."[20] A manufacturer's ability to change a label via the CBE process is not absolute, however. The FDA reviews CBE submissions and retains the power to reject proposed changes that do not meet the regulatory standards.[21]

18 21 C.F.R. § 314.3(b).

19 *Wyeth*, 555 U.S. at 569, 129 S.Ct. 1187.

20 73 Fed. Reg. at 49,606.

21 *See* 21 C.F.R. § 314.70(c)(4)-(6).

Second, manufacturers can implement "major changes" to a label by filing a so-called "Prior Approval Supplement" ("PAS").[22] Unlike a CBE change, a PAS change requires prior FDA approval before it can be implemented.[23] The key distinction for present purposes is that a proposed label change that qualifies for a CBE supplement—including a proposal to "add or strengthen a contraindication, warning, precaution, or adverse reaction"—need not be submitted through the PAS process and does not require prior FDA approval.[24]

22 *Id*. § 314.70(b).

23 *Id*. § 314.70(b)(3).

24 *Id*. § 314.70(b)(2)(v)(A); *id.* § 314.70(c)(6)(iii)(A).

It is important to recognize, however, that the FDA does

not simply approve warnings out of an abundance of caution whenever the manufacturer posits a theoretical association between drug use and an adverse event. As the FDA has recognized, "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug."[25] Moreover, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance."[26] Accordingly, the FDA will reject a PAS application or CBE amendment if there is insufficient evidence of a causal link between drug use and the adverse event.[27]

25 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

26 *Id*.

27 *Id.*

C. Fosamax Labeling History

Both Merck and the FDA have long been aware that antiresorptive drugs like Fosamax could theoretically increase the risk of atypical femoral fractures. The question that both Merck and the FDA faced in the years following the drug's approval was whether the developing evidence of a causal link between Fosamax and atypical fractures was strong enough to require adding a warning to the Fosamax drug label. As explained further in Section II of this opinion, the primary question in this appeal is whether, prior to September 2010, the FDA would have rejected an attempt by Merck to unilaterally amend the Fosamax label (via a CBE submission) to include a warning about the risk of atypical femoral fractures. The following evidence bears on that question.

***275** i. Early Studies Suggest a Possible Link Between Fosamax and Atypical Femoral Fractures

During Fosamax's development, Merck scientists and third-party researchers discussed the possibility that antiresorptive drugs could inhibit a bone's ability to repair microdamage, potentially leading to stress fractures. In 1992, prior to FDA approval, Merck informed the FDA that "antiresorptive agents may inhibit microdamage repair by preventing ... bone resorption at the sites of microdamage."[28] Nonetheless, when the FDA approved Fosamax in 1995 for the treatment of osteoporosis in postmenopausal women, it did not require Merck to include a warning about bone fractures. Nor did it do so in 1997, when it approved Fosamax for the prevention of osteoporosis in postmenopausal women.

28 A 1774.

Between 1995 and 2010, scores of case studies, reports, and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures. Plaintiffs have directed our attention to six such studies from this period. None of these studies, however, concluded that Fosamax caused bone fractures, or even that Fosamax use was definitively associated with atypical fractures. Rather, they variously stated that Fosamax use "may ... potentially" increase the risk of fracture[29] or "may be associated" with insufficiency fractures,[30] or that certain findings "raise[d] the possibility" that Fosamax use led to fractures.[31] Merck's assertion that the link between Fosamax and fracturing "remained hypothetical and unsubstantiated"[32] may be an understatement, but not even Plaintiffs suggest that there was definitive proof of a causal connection at this time.

29 A 1258.

30 A 1237.

31 A 1243.

32 Merck Br. 8.

Merck kept the FDA informed of these and other studies suggesting a possible association between bisphosphonates and fractures, either citing or submitting

them in communications with the agency. In March 2008, Merck submitted a periodic safety update to the FDA that included over 30 pages of information regarding atypical femur fractures and suppression of bone turnover. Merck reported that "recent publications" had "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures."[33] It also stated "the reporters related these findings to severely suppressed bone turnover that may develop during long-term" use of Fosamax.[34] Later that month, Merck forwarded to the FDA a letter published in the *New England Journal of Medicine* describing a "potential link between [bisphosphonate] use and low-energy fractures of the femur."[35]

33 A 2597.

34 *Id*.

35 A 1928-33.

In June 2008, the FDA informed Merck that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates."[36] It also stated that it was "concerned about this developing safety signal."[37] The FDA asked Merck to submit any investigations it had conducted or reports it had received regarding femoral fractures. Merck promptly complied.

36 A 1935.

37 *Id*.

***276** ii. Merck Attempts to Amend the Fosamax Label

In September 2008, while the FDA was analyzing Merck's data, Merck submitted a PAS to the FDA. As discussed above, a PAS is a label-change request that, unlike a CBE submission, requires prior approval from the FDA.[38] In the PAS, Merck proposed to add language to both the Warnings & Precautions and the Adverse Reactions sections of the label to address atypical femoral fractures. Merck explained that "[i]t is not possible with the present data to establish whether treatment with" Fosamax "increases the risk of [these] ... low-energy subtrochanteric and/or proximal shaft fractures."[39] But because of the temporal association between these fractures and Fosamax use, Merck believed that it was "important to include an appropriate statement about them in the product label" to "increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications."[40]

38 *See supra* Section I.B.

39 A 1349.

40 *Id*.

Merck proposed adding the following language to the Warnings and Precautions section of the label:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual

benefit/risk assessment.[41]

41 A 1371.

Merck also proposed adding "low-energy femoral shaft fracture" to the list of reported adverse reactions in the Adverse Reactions section of the label,[42] as well as the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh."[43] In support of its PAS application, Merck included an analysis of femur fractures in Fosamax users and cited to nine articles reporting cases of low-energy femoral fractures in Fosamax users.

42 A 1383.

43 A 2742.

In April 2009, Merck representatives held a telephone conversation with Dr. Scott Monroe of the FDA. According to Merck's internal notes, Dr. Monroe stated that the FDA could agree to add language in the Adverse Reactions section of the ***277** label, but that Merck's "elevation of this issue to a precaution in the labeling" was prolonging review.[44] The FDA wanted "to approach the issue of a precaution from the [perspective] of all bisphosphonates" and was "working with the Office of Safety and Epidemiology to do so."[45] Dr. Monroe also stated that because "the conflicting nature of the literature does not provide a clear path forward, ... more time will be need[ed] for FDA to formulate a formal opinion on the issue of a precaution around these data."[46]

44 A 1970-71.

45 A 1971.

46 *Id*.

Later in April 2009, an FDA liaison sent Merck an e-mail stating that the FDA was not prepared to include language about low-energy femoral fractures in the Warnings and Precautions section of the label and would only approve a reference to atypical fractures in the "Adverse Reaction" section.[47] The FDA asked Merck to "hold off on the [Warnings and Precautions] language at this time" so that drug evaluators could "then work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide on language for a [Warnings and Precautions] atypical fracture language, if it is warranted."[48]

47 A 1498.

48 *Id*.

In May 2009, the FDA sent Merck a "Complete Response" letter, authored by Dr. Monroe. In the Complete Response, the FDA approved the addition of "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section, but the FDA rejected Merck's proposed addition to the Warnings and Precautions section. Because the parties vigorously dispute the grounds for this rejection, it is worth excerpting the relevant portion of the FDA notice in full:

> We have completed the review of your [PAS] applications, as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.
> 1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.[49]

49 A 1500-01.

The outcome of this case hinges in large part on how one reads (or really, on how a reasonable jury could read) this language in conjunction with the FDA's accompanying actions and communications. Plaintiffs claim that the FDA was objecting only to Merck's use of the imprecise and potentially misleading term "stress fractures," and that the FDA would have approved a proposed warning that specifically discussed the risk of atypical femoral fractures while eliminating the general references to stress fractures. Merck claims that this letter, along with the FDA's other communications, demonstrates that the FDA simply did not believe there was sufficient evidence of a causal link between Fosamax use and atypical fractures, and would have ***278** rejected *any* proposed warning relating to such a risk.

iii. The FDA Revises its Position on the Link Between Bisphosphonates and Atypical Femur Fractures

In March 2010, after reviewing the data submitted by Merck and other manufacturers, the FDA stated publicly that the data reviewed to date had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."[50] The FDA announced that it would work with an outside expert task force to gather additional information.

50 A 1508.

In September 2010, the task force published a report finding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture."[51] The report stated that although there was an association between long-term bisphosphonate use and atypical fractures, the association had not been proven to be causal. The FDA responded by issuing a Drug Safety Communication stating that, "[a]lthough it is not clear if bisphosphonates are the cause [of fractures], these unusual femur fractures have been identified in patients taking these drugs."[52] Regarding the task force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports" and would be "considering label revisions."[53]

51 A 1167.

52 A 1512.

53 *Id.*

In October 2010, the FDA announced that it would require all bisphosphonate manufacturers to add information regarding the risk of atypical femoral fractures to the Warnings and Precautions section of the drug labels, based on the FDA's conclusion that "these atypical fractures may be related to long-term ... bisphosphonate use."[54] It reiterated that it was still "not clear if bisphosphonates are the cause," but noted that "these unusual femur fractures have been predominantly reported in patients taking bisphosphonates."[55] In a conference call accompanying the announcement, the FDA's Deputy Director of the Office of New Drugs stated that the task force report made the FDA "confident" that atypical femur fractures are "potentially more closely related to" long-term use of bisphosphonates "than [the FDA] previously had evidence for."[56]

54 A 1118. The FDA also announced that it would require a new Limitations of Use statement in the Indications and Usage section of the labels to "describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis." *Id.*

55 *Id.*

56 A 1396.

The same day, the FDA wrote to Merck requesting that Merck add the following language to the Warnings and Precautions section of the Fosamax label:

Atypical Subtrochanteric and Diaphyseal Femoral Fractures:

> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who ***279** have not been treated with bisphosphonates.
>
> Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.[57]

57 A 1516-17.

Merck responded by proposing additional language that, according to Merck, was intended to make clear that doctors should attempt to rule out stress fractures. The proposal contained five specific references to "stress fractures." The FDA responded to this proposal by eliminating every instance of the phrase "stress fractures." In rejecting Merck's proposal, the FDA explained that "the term 'stress fracture' was considered and not accepted. The Division believes that for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use."[58] The FDA subsequently approved language nearly identical to its original October 2010 proposal. That language was added to the Fosamax label in January 2011 and has remained there since.

58 A 1540.

D. Procedural History

After the label change, patients who had taken Fosamax and suffered atypical femur fractures filed lawsuits against Merck throughout the country. In May 2011, the Judicial Panel on Multidistrict Litigation consolidated these cases for pre-trial administration in a multi-district litigation ("MDL") in the District of New Jersey.[59] Since then, the MDL has been assigned to three different district judges[60] and has swelled to over 1,000 cases, each involving a separate patient who allegedly suffered a femur fracture after taking Fosamax.

59 *In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F.Supp.2d 1355 (J.P.M.L. 2011) (hereinafter, "*Fosamax MDL Order*").

60 The MDL is currently assigned to the Honorable Freda Wolfson.

Although no two complaints in the MDL are identical, all of the actions "share questions of fact arising from similar allegations that use of Fosamax ... caused femur fractures or similar bone injuries."[61] The individual Plaintiffs in this appeal all allege that they were injured before September 14, 2010, the date the outside expert task force published its report documenting an association between bisphosphonate use and atypical femur fractures. According to Plaintiffs,[62] the ***280** complaints filed by this cohort generally include a state-law products liability claim for failure to warn, alleging that Fosamax was defective because Merck failed to warn Plaintiffs and their physicians about the risk of atypical femur fractures. Many complaints also claim that Fosamax was defectively designed because the risks of Fosamax exceeded the benefits, or because Fosamax was unreasonably dangerous or more dangerous than an ordinary consumer would expect. Many complaints also include claims for, among other causes of action, negligence, negligent misrepresentation, breach of express and implied warranties, unjust enrichment, punitive damages, and violations of state consumer fraud and deceptive trade practice statutes.[63]

61 *Fosamax MDL Order*, 787 F.Supp.2d at 1356.

62 This appeal involves over 500 related cases, and the parties have wisely chosen not to include each complaint in the record. We are therefore necessarily reliant on the parties for information regarding the nature, prevalence and commonality of the plaintiffs' claims.

63 Although the complaints exclusively plead state-law causes of action, the actions are in federal court on diversity grounds.

Merck has argued since the inception of the MDL that Plaintiffs' state-law failure-to-warn claims are preempted by FDA regulations. The District Court decided to address preemption after developing a full record in a bellwether trial, the so-called *Glynn* trial. Typical of all plaintiffs in this MDL, the lead plaintiff in *Glynn* claimed that she suffered an atypical femur fracture that was proximately caused by Merck's failure to include adequate fracture warnings on the Fosamax label.[64] Merck moved for judgment as a matter of law on preemption grounds before and during trial, but the District Court reserved judgment.[65] The jury returned a verdict for Merck on the merits, finding that Ms. Glynn failed to prove by a preponderance of the evidence that she experienced an atypical femur fracture.[66] Despite this verdict, the District Court announced that it would still decide whether the Glynns' claims were preempted.[67]

64 Although the *Glynn* plaintiffs brought multiple claims, the only one they actually tried to verdict was a failure-to-warn claim. *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (Glynn v. Merck Sharp & Dohme Corp.)*, 951 F.Supp.2d 695, 700 & n.5 (D.N.J. 2013) (hereinafter, "*Glynn*").

65 *Id*. at 700-701.

66 *Id*. at 701.

67 *Id*.

In June 2013, the District Court issued an opinion concluding that the Glynns' failure-to-warn claim was preempted by federal law. Applying the Supreme Court's decision in *Wyeth*, the court stated that state-law failure-to-warn claims are preempted when "there is 'clear evidence that the FDA would not have approved a change' to the prescription drug's label."[68] The District Court concluded that the Glynns' claim was preempted because the FDA's May 2009 denial of Merck's request to add language about atypical femur fractures to the Warnings and Precautions section of the label was "clear evidence that the FDA would not have approved a label change to the Precautions section of the label prior to Ms. Glynn's injury."[69]

68 *Glynn*, 951 F.Supp.2d at 702 (quoting *Wyeth*, 555 U.S. at 571, 129 S.Ct. 1187).

69 *Id*. at 703.

Shortly after the *Glynn* decision, Merck moved for an order to show cause why all the cases in the MDL alleging injuries prior to the release of the September 2010 task force report should not be dismissed on preemption grounds. Plaintiffs opposed the motion on the ground that resolving their claims through a show-cause procedure would violate their due process right to individual trials. In August 2013, the District Court issued an Order to Show Cause why the pre-September 2010 claims ***281** should not be dismissed on preemption grounds, and the parties submitted briefing. Although both sides disputed the propriety of the show-cause procedure and the substance of Merck's preemption arguments, the parties and the District Court all agreed that Federal Rule of Civil Procedure 56 "provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s)."[70]

70 *In re Fosamax (Alendronate Sodium): Prods. Liab. Litig.*, MDL No. 2243, Master Dkt. No. 08-08 (JAP)(LHG), 2014 WL 1266994, at *8 (D.N.J. Mar. 26,

2014) (hereinafter, "*Summary Judgment Order*"). The parties continue to agree that Rule 56 is the proper framework to apply, although they dispute how to apportion the parties' burdens of production and persuasion.

After briefing, the District Court granted summary judgment to Merck and ruled that all claims made by plaintiffs who were injured prior to September 14, 2010 were preempted under *Wyeth*. Specifically, the court ruled that: (1) Merck had met its initial burden of demonstrating that there was no genuine issue of material fact as to preemption in *Glynn*, and that Plaintiffs therefore bore the burden of producing a genuine issue for trial; (2) Plaintiffs had failed to create a genuine issue as to preemption; (3) it was proper to use a show-cause proceeding to apply the *Glynn* preemption ruling to other MDL cases; (4) Plaintiffs' design-defect and other non-warning claims were also preempted because they sounded in failure to warn; and (5) Plaintiffs' alternate theories that Merck should have added information about fractures to the Adverse Reactions section of the label prior to 2009 and should have warned that Fosamax's long-term benefits were limited should be dismissed.

With respect to the failure-to-warn claims, the District Court reiterated its conclusion from *Glynn* that "the fact that the FDA never required [Merck] to submit new language or change the label demonstrates that the FDA did not think that the label should have been changed at that time."[71] This evidence "remain[ed] unchanged" and provided "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning."[72] As to the non-failure-to-warn claims (including claims for design defect, negligence, fraud, breach of warranty, deceptive trade practice, and unjust enrichment), the District Court concluded that that these claims "are based entirely on the premise that Fosamax had risks which should have been disclosed to consumers" and therefore "ultimately hinge[ ] on the adequacy of Fosamax's warning."[73] Because these claims "rise and fall with a claim for failure to warn," they too were preempted.[74] This appeal followed.[75]

71 *Id*. at *16 (quoting *Glynn*, 951 F.Supp.2d at 703-04) (alterations omitted).

72 *Id*.

73 *Id*. at *12, *14.

74 *Id*. at *12, *14.

75 This appeal involves only those Plaintiffs who alleged that they were injured before September 14, 2010. *See*, *e.g.*, *id*. at *17 (granting summary judgment to Merck on "all claims made by the Plaintiffs ... with injuries that occurred prior to September 14, 2010"). Plaintiffs inform us that there are "approximately 570 remaining cases in the MDL involving plaintiffs who were injured after September 14, 2010." Pls. Br. 8; *see also* A 2067-80. In June 2015, the District Court conditionally dismissed these remaining actions without prejudice, concluding that they "are based on the alleged inadequacy of the pre-2011 Fosamax label" and that our decision here would "determine whether the claims of the remaining Plaintiffs in this litigation ... remain viable or not." A 2065. We express no view regarding the effect of today's ruling on the remaining plaintiffs' claims.

*282 II. LEGAL BACKGROUND

The primary issue in this case is whether Plaintiffs' state-law failure-to-warn claims are preempted by federal law under the Supreme Court's decision in *Wyeth*. This is not a straightforward determination. *Wyeth* says only that a claim is preempted when there is "clear evidence" that the FDA would not have approved a label change. This standard is cryptic and open-ended, and lower courts have struggled to make it readily administrable. This appeal, however, requires us to do so. To assess whether Merck is entitled to summary judgment on its affirmative preemption defense, we must answer two questions: What is "clear evidence"? And who should determine whether clear evidence exists?

For the following reasons, we conclude that (1) the term "clear evidence" refers solely to the applicable standard of proof, and (2) the ultimate question of whether the FDA would have rejected a label change is a question of fact for the jury rather than for the court. By describing the

ultimate question as one of fact for the jury, we do not mean to suggest that summary judgment is categorically unavailable to a manufacturer asserting a preemption defense. When there is no genuine issue of material fact—that is, when no reasonable jury applying the clear-evidence standard of proof could conclude that the FDA would have approved a label change—the manufacturer will be entitled to judgment as a matter of law. We simply hold that, at the summary judgment stage, the court cannot decide for itself whether the FDA would have rejected a change, but must instead ask whether a reasonable jury could find that the FDA would have approved the change.

A. Federal Preemption Doctrine: Impossibility Preemption and the Supreme Court's Decision in *Wyeth v. Levine*

i. Impossibility Preemption

[1] [2] [3]The Supremacy Clause establishes that federal law "shall be the supreme Law of the Land."[76] The Supremacy Clause, therefore, preempts "state laws that 'interfere with, or are contrary to,' federal law."[77] There are several varieties of preemption; the one at issue here is called "conflict" or "impossibility" preemption. Impossibility preemption applies, and state law must give way, when "it is 'impossible for a private party to comply with both state and federal requirements.' "[78] "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."[79]

76 U.S. Const., Art. VI, cl. 2.

77 *Hillsborough Cty., Florida v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985) (quoting *Gibbons v. Ogden*, 22 U.S. (9 Wheat.) 1, 211, 6 L.Ed. 23 (1824)).

78 *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618, 131 S.Ct. 2567, 180 L.Ed.2d 580 (2011) (quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S.Ct. 1483, 131 L.Ed.2d 385 (1995)).

79 *Id*. at 620, 131 S.Ct. 2567.

In this case, Plaintiffs claim that state law obligated Merck to add a warning about atypical femur fractures to the Fosamax label. At issue is whether federal law—here, FDA regulations—prevented Merck from adding the type of warnings that Plaintiffs claim were required under state law. The Supreme Court confronted a similar question in *Wyeth*, and its opinion governs our analysis here.

***283** ii. The *Wyeth* Decision

In *Wyeth*, the Supreme Court addressed whether and to what extent state-law failure-to-warn claims are preempted by the FDCA and federal drug-labeling regulations. The Court held that failure-to-warn claims against drug manufacturers generally are not preempted by FDA approval of the drug's warning label. But such a claim *is* preempted by federal law when there is "clear evidence" that the FDA would not have approved the warning that a plaintiff claims was necessary.

The plaintiff in *Wyeth* developed gangrene when a physician's assistant injected her with the antinausea drug Phenergan. She brought a state-law failure-to-warn claim against Wyeth, the manufacturer of Phenergan, for failing to provide an adequate warning about the risks involved with various methods of administering the drug. A jury concluded that the plaintiff's injury was caused by Wyeth's inadequate warning label. Wyeth argued on appeal that the state-law failure-to-warn claims were preempted because it was impossible to comply with both state-law warning duties and federal labeling obligations.[80]

80 *Wyeth*, 555 U.S. at 559-64, 129 S.Ct. 1187.

The Supreme Court rejected Wyeth's argument. It began by citing the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."[81] Under this rule, a manufacturer "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[82] Thus, when the risks of a particular drug use become apparent, the manufacturer

has "a duty to provide a warning that adequately describe[s] that risk."[83]

81 *Id.* at 570-71, 129 S.Ct. 1187.

82 *Id*. at 571, 129 S.Ct. 1187.

83 *Id*.

In response to Wyeth's contention that federal law made it impossible to add the warnings the plaintiff claimed were necessary, the Court observed that drug manufacturers are allowed to strengthen an FDA-approved warning label without FDA approval through the CBE process.[84] Wyeth therefore could not establish impossibility preemption because the CBE regulation "permitted [Wyeth] to provide ... a warning [of the risk of gangrene] before receiving the FDA's approval."[85]

84 *Id.* at 568, 129 S.Ct. 1187.

85 *Id*. at 571, 129 S.Ct. 1187.

[4]The Supreme Court cautioned, however, that the mere availability of a CBE label amendment would not always defeat a manufacturer's preemption defense, because the FDA "retains authority to reject labeling changes."[86] Thus, where there is "clear evidence that the FDA would not have approved a change" to the label, federal law preempts state-law claims premised on the manufacturer's failure to make that change.[87] Impossibility preemption applies in that instance because the manufacturer would be legally prevented by the FDA from taking the very action that state law ostensibly requires.[88]

86 *Id*.

87 *Id*.

88 If a manufacturer retains a warning that the FDA has rejected, the drug may be deemed "misbranded" in violation of federal law. *See* 21 U.S.C. § 352(a) (drug shall be considered misbranded "[i]f its labeling is false or misleading in any particular"); A 1501 (FDA letter rejecting Merck's PAS proposal to amend the Fosamax label and stating that "[t]hese products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications").

***284** The manufacturer in *Wyeth* could not take advantage of the clear-evidence exception because it had "offered no such evidence" that the FDA would have rejected the warning sought by the plaintiff.[89] But the Supreme Court made it clear that if a manufacturer does present "clear evidence" that the FDA would reject a plaintiff's proposed warning, it would have a complete preemption defense to any state-law failure-to-warn claims.

89 *Wyeth*, 555 U.S. at 571-72, 129 S.Ct. 1187.

In this case, Merck claims that the FDA's 2009 rejection of its proposed label amendment is just such "clear evidence."

B. Defining "Clear Evidence"

Courts applying the *Wyeth* preemption rule confront an immediate question: what is "clear evidence that the FDA would not have approved a change"? The *Wyeth* Court did not define the "clear evidence" standard or explain how courts should apply it. The only guidance the Court offered was to call impossibility preemption a "demanding defense."[90] In the absence of explicit direction or a coherent doctrinal framework, lower courts have been understandably reluctant to articulate firm definitions of the standard or its requirements. For example, several of our sister circuits have decided preemption cases by simply treating the facts of *Wyeth* as a yardstick: if the evidence for FDA rejection in a given case is less compelling than the manufacturer's evidence in *Wyeth*, the thinking goes, then there is clear evidence that the FDA would not have approved a label change and the manufacturer's preemption defense fails.[91] Many

district courts have adopted a similar, if more complex, approach of exhaustively surveying the post-*Wyeth* case law and then testing the facts of a particular case against prior decisions.[92] Both approaches produce valid outcomes in individual cases, but neither clarifies or builds out the doctrine. The result is an anomaly in our preemption jurisprudence: the number of cases applying the clear evidence standard continues to grow, yet "the clear evidence standard remains undefined."[93]

90 *Id.* at 573, 129 S.Ct. 1187.

91 *See Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392-96 (7th Cir. 2010) (stating that *Wyeth* provides an "intellectual anchor" because "if the evidence here is less compelling than it was in [*Wyeth*], we will not find preemption," and holding that preemption was unwarranted because the manufacturer's evidence was not "any more compelling"); *Gaeta v. Perrigo Pharms. Co.*, 630 F.3d 1225, 1235-37 (9th Cir. 2011) (observing that "the only guidance this court has is that the evidence presented in [*Wyeth*] was insufficient to meet the clear evidence standard" and holding that preemption was unwarranted "[b]ecause the evidence presented by Perrigo in this case is no more compelling than the evidence considered and rejected by the Supreme Court in [*Wyeth*]" (abrogated on other grounds, *PLIVA*, 564 U.S. 604, 131 S.Ct. 2567)).

92 *See, e.g., In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F.Supp.3d 1108 (S.D. Cal. 2015); *Seufert v. Merck Sharp & Dohme Corp.*, 187 F.Supp.3d 1163 (S.D. Cal. 2016).

93 *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F.Supp.3d at 1119.

Today, we hold that the Supreme Court intended to announce a standard of proof when it used the term "clear evidence" in *Wyeth*.

[5] [6]The *Wyeth* Court articulated the "clear evidence" exception as follows: "[A]bsent 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." ***285** [94] This formula has three components: (1) a legal rule that defines the circumstances in which a manufacturer is absolved of state-law liability (it must be impossible for the manufacturer to comply with both federal and state requirements); (2) a factual showing that satisfies the legal rule (the FDA would not have approved the proposed label change); and (3) a standard of proof that specifies how convincing the factual showing must be (the manufacturer must show that the FDA would not have approved the proposed label change by "clear evidence"). The term "clear evidence" therefore does not refer directly to the *type* of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate. Rather, it specifies how *difficult* it will be for the manufacturer to convince the factfinder that the FDA would have rejected a proposed label change. The manufacturer must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by "clear evidence."

94 555 U.S. at 571, 129 S.Ct. 1187.

Our conclusion that the *Wyeth* Court intended the term "clear evidence" to denote a standard of proof is supported by the Supreme Court's prior usage of the term. For example, the Court has consistently held that a complainant alleging official government misconduct must present "clear evidence" of unlawful behavior.[95] "Clear evidence" in this context is understood to be a standard of proof, rather than a condition on the type of facts that must be proven.[96] Similar examples are found in the bankruptcy and patent settings.[97]

95 *See, e.g., United States v. Chemical Found., Inc.*, 272 U.S. 1, 14-15, 47 S.Ct. 1, 71 L.Ed. 131 (1926) ("The presumption of regularity supports the official acts of public officers, and, in the absence of clear evidence to the contrary, courts presume that they have properly discharged their official duties."); *United States v. Armstrong*, 517 U.S. 456, 465, 116 S.Ct. 1480, 134 L.Ed.2d 687 (1996) (criminal defendant alleging racially discriminatory prosecution must present "clear evidence" that prosecutorial policy had discriminatory effect and purpose); *Reno v. American-Arab Anti-Discrimination Comm.*, 525 U.S. 471, 489, 119 S.Ct. 936, 142 L.Ed.2d 940 (1999) (selective prosecution claim requires "clear evidence" of unlawful action).

96 *See Reno*, 525 U.S. at 489, 119 S.Ct. 936 (stating that clear evidence is "the standard for proving" a selective prosecution claim); *United States v. Jarrett*, 447 F.3d 520, 525 (7th Cir. 2006) (describing clear evidence as "[t]he standard of proof" for selective prosecution claims).

97 *See Oriel v. Russell*, 278 U.S. 358, 362-63, 49 S.Ct. 173, 73 L.Ed. 419 (1929) (when a party seeks turnover in a bankruptcy proceeding, "[a] mere preponderance of evidence ... is not enough" and the court deciding the motion "should therefore require clear evidence"); *Microsoft v. I4I Ltd. P'ship*, 564 U.S. 91, 97, 113-14, 131 S.Ct. 2238, 180 L.Ed.2d 131 (2011) (Federal Circuit's interpretation of Patent Act as requiring "clear evidence" of invalidity accurately stated the statutory standard of proof).

Nor must we look far to discern the meaning of "clear evidence," as Supreme Court usage confirms that the term is synonymous with "clear and convincing evidence."[98] The latter is a well-recognized intermediate standard of proof—more demanding than preponderance of the evidence, but less demanding than ***286** proof beyond a reasonable doubt. Black's Law Dictionary defines clear and convincing evidence as "evidence indicating that the thing to be proved is highly probable or reasonably certain."[99] We adopt that definition here. It is consistent with both settled understanding and *Wyeth*' s instruction that the clear-evidence test is a "demanding defense" meant to represent a longstanding "presumption against pre-emption."[100]

98 *See Microsoft*, 564 U.S. at 97, 113-14, 131 S.Ct. 2238 (equating Federal Circuit's "clear evidence" standard with "clear and convincing" standard); *Oriel*, 278 U.S. at 362-63, 49 S.Ct. 173 (equating "clear evidence" with "clear and convincing evidence"); *accord Ramsey v. United Mine Workers of Am.*, 401 U.S. 302, 307-09, 311, 91 S.Ct. 658, 28 L.Ed.2d 64 (1971) (interpreting statute requiring "clear proof" as requiring "clear and convincing evidence").

99 Black's Law Dictionary 674 (10th ed. 2009).

100 *Wyeth*, 555 U.S. at 571-73, 565 n.3, 129 S.Ct. 1187.

[7]We therefore conclude that for a defendant to establish a preemption defense under *Wyeth*, the factfinder must conclude that it is highly probable that the FDA would not have approved a change to the drug's label.

C. Whether the FDA Would Have Rejected a Label Change is a Question of Fact for the Jury

Once "clear evidence" is understood as a standard of proof rather than a condition on the type of facts to be proven, the *Wyeth* test narrows to a single inquiry: would the FDA have approved the label change that Plaintiffs argue was required?

[8]Oral argument in this case revealed a fundamental yet unexplored disagreement between the parties. Merck claimed that the *Wyeth* preemption test presents a pure question of law that must be decided by a court, not a jury. Plaintiffs argued that *Wyeth* preemption poses a mixed question of fact and law that may require jury factfinding in appropriate circumstances. The distinction is crucial in this case because it dictates the course of our summary judgment analysis. If the question of whether the FDA would have rejected Plaintiffs' proposed warning is a question of law for the court, then we may simply answer it ourselves; but if it is a question of fact for the jury, then we must instead attempt to anticipate the range of answers that could be given by reasonable jurors applying the clear evidence standard and then determine whether summary judgment is appropriate. Having reviewed the case law and the parties' supplemental briefing on the issue, we conclude that the question of whether the FDA would have rejected a proposed label change is a question of fact that must be answered by a jury.[101] The court's role at the summary judgment stage is therefore limited to determining whether there are genuine issues of material fact that preclude judgment as a matter of law.

101 Our discussion of the allocation of decision-making authority, both here and elsewhere in this Opinion, applies in cases tried to a jury. In a bench trial, of course, judicial factfinding will be both appropriate and necessary.

i. Conflict Preemption Can Require Fact Determinations by a Jury

Merck makes two general, threshold arguments in favor of treating *Wyeth* preemption as a purely legal question to be answered by the court.

First, Merck notes that the vast majority of courts applying *Wyeth* have assumed, either explicitly or implicitly, that *Wyeth* preemption presents a question of law. This observation is only somewhat accurate and wholly unpersuasive.

Wyeth does not indicate whether the "clear evidence" test poses a legal or factual question. Nor is it possible to divine a clear answer from the Supreme Court's application of the test in *Wyeth* itself.[102] ***287** However, the Supreme Court did decide that the evidence presented in *Wyeth* was not sufficient to pass the clear evidence test. Therefore, in light of the Court's definitive holding that the evidence in *Wyeth* did not pass muster, the many federal courts that have applied the *Wyeth* preemption test have simply compared the evidence presented in their cases to the evidence presented in *Wyeth*. For example, in *Mason v. SmithKline Beecham Corp.*, the Seventh Circuit walked through the record evidence and concluded that, "in light of the extensive showing required by [*Wyeth*]," the manufacturer "did not meet its burden of demonstrating by clear evidence that the FDA would have rejected a label change."[103] The Ninth Circuit took a similar approach in *Gaeta v. Perrigo Pharmaceuticals Co.*, and explicitly stated that since "the only guidance this court has is that the evidence presented in [*Wyeth*] was insufficient to meet the clear evidence standard," the manufacturer would not meet the clear evidence standard if the "evidence in this case [is] less compelling than [that] in [*Wyeth*]."[104] Many other circuits have followed this approach and have found no preemption because the evidence in those cases fell short of the record in *Wyeth*.[105]

102 Had *Wyeth* come up on appeal from a grant of summary judgment, for example, the Court would have been forced to address whether the question of what the FDA would have done should be answered by a court or by a jury. But *Wyeth* was an appeal of a post-trial motion for judgment, following a full jury trial and post-verdict proceedings in which the trial court made explicit fact findings, based on the trial record, directed at the preemption issue. *Wyeth*, 555 U.S. at 561-63, 129 S.Ct. 1187. The Supreme Court concluded on the basis of that complete record that there was "no ... evidence" that the FDA would have rejected a warning. *Id.* at 572, 129 S.Ct. 1187. The combination of (1) a complete fact record that (2) contained zero evidence to support preemption eliminated the need for remand, and thereby obviated the need to explain which judicial actor should make preemption-related findings in the first instance. And since the complete record contained *no evidence* whatsoever indicating that the FDA would not have approved a label change, the Supreme Court had no reason to consider whether a jury could have reached a contrary conclusion.

103 *Mason*, 596 F.3d at 393-96.

104 *Gaeta*, 630 F.3d at 1235-36.

105 *See, e.g.*, *Demahy v. Actavis, Inc.*, 593 F.3d 428, 446 (5th Cir. 2010) ("The record here contains nothing, let alone 'clear evidence,' that suggests the FDA would have rejected a labeling proposal from Actavis."); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 610-11 (8th Cir. 2009) ("The record contains nothing, let alone 'clear evidence,' to suggest the FDA would have rejected a labeling proposal from any of them."); *but see Miller v. SmithKline Beecham Corp.*, 381 Fed.Appx. 776 (10th Cir. 2010) (unpublished) (without any prior discussion, remanding "to give the [district] court the opportunity to make evidentiary findings and analyze the record in light of [*Wyeth's*] new 'clear evidence' standard").

It is possible to characterize this approach as a tacit acknowledgment that the "clear evidence" test is a legal question to be answered directly by the court. *Mason*, for example, was an appeal of a grant of summary judgment, but the court did not engage in a Rule 56 disputed-facts analysis or consider whether a reasonable jury could reach a contrary conclusion. At the same time the court also did not explain why the *Wyeth* test should be resolved by the court in the first instance. We do not lightly discount the wisdom of our sister circuits and the district courts that have grappled with these issues. But there is a difference between rejecting another court's considered judgment, on the one hand, and taking up an issue that has not been

thoroughly analyzed, on the other. Furthermore, the approach taken by our sister circuits would be entirely consistent with our decision that the "clear evidence" test is a fact question that is ultimately for a jury to decide. After all, by comparing ***288** the evidence presented in these cases with the evidence presented in *Wyeth*, these circuits are in fact engaging in a summary judgment analysis, even if they do not name it.

Second, Merck asserts that conflict preemption *always* presents a pure question of law. To be sure, we have made numerous offhand statements that seem to support Merck's position.[106] And as Merck points out, several district courts relying on similar language have concluded, albeit without substantial analysis, that a manufacturer's entitlement to the *Wyeth* preemption defense is a question of law for the court rather than the jury.[107]

106 *See*, *e.g.*, *In re Federal-Mogul Global Inc.*, 684 F.3d 355, 364 n.16 (3d Cir. 2012) ("The scope of preemption presents a pure question of law, which we review *de novo*."); *Horn v. Thoratec Corp.*, 376 F.3d 163, 166 (3d Cir. 2004) ("This Court also exercises plenary review over a district court's preemption determination, as it is a question of law.").

107 *See Dobbs v. Wyeth Pharms.*, 797 F.Supp.2d 1264, 1267 (W.D. Okla. 2011); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F.Supp.3d at 1114.

The "rule" Merck cites, however, is one of thumb rather than law. It is true that *most* preemption cases present purely legal questions—for example, whether Congress intended to preempt state law, how to interpret the scope of an express preemption provision, or whether two regulatory schemes are facially incompatible. But it is equally clear that preemption can be, and sometimes must be, a fact question for the jury.

The Supreme Court's opinion in *Boyle v. United Technologies Corp.*[108] illustrates the distinction. In *Boyle*, as in *Wyeth*, the Supreme Court defined the scope of conflict preemption in a particular setting and announced the factual showing that a defendant must make to prove the affirmative preemption defense. Specifically, the Court held that "[l]iability for design defects in military equipment cannot be imposed, pursuant to state law, when (1) the United States approved reasonably precise specifications; (2) the equipment conformed to those specifications; and (3) the supplier warned the United States about the dangers in the use of the equipment that were known to the supplier but not to the United States."[109] The Court clarified that "whether the facts establish the conditions for the defense is a question for the jury."[110] The proper question on summary judgment, therefore, was whether a "reasonable jury could, under the properly formulated defense, have found for the petitioner on the facts presented."[111] It would be error, the Court said, for a court to "assess[ ] on its own whether the defense had been established."[112]

108 487 U.S. 500, 108 S.Ct. 2510, 101 L.Ed.2d 442 (1988).

109 *Id*. at 512, 108 S.Ct. 2510.

110 *Id*. at 514, 108 S.Ct. 2510.

111 *Id*.

112 *Id*.

While our court has not gone so far as to declare that any one species of preemption defense categorically requires jury factfinding, we have acknowledged that the availability of the defense can turn on questions of fact. In *MD Mall Associates, LLC v. CSX Transportation, Inc.*,[113] we determined that the question of whether state-law storm water trespass claims conflicted with federal railroad-safety regulations had to be addressed "under the circumstances of this particular case."[114] We ***289** therefore held that whether the defendant railroad could reasonably comply with federal drainage requirements while also complying with Pennsylvania law regarding storm water trespass "is a question of fact."[115] Having so concluded, we remanded for further development of the factual record.

113 715 F.3d 479 (3d Cir. 2013).

114 *Id*. at 496 (alteration omitted) (quoting *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 373, 120 S.Ct. 2288, 147 L.Ed.2d 352 (2000)).

115 *Id*.

Boyle and *MD Mall* confirm that the availability of a conflict preemption defense is not automatically a question of law that must be kept from the jury. The question, therefore, is whether there are independent jurisprudential or practical reasons to conclude that *Wyeth* preemption, specifically, requires a legal or a factual determination.

ii. Whether the FDA Would Have Approved a Label Change is a Factual Question Appropriate for the Jury

There are no general, hard-and-fast rules that we can use to distinguish fact questions from legal ones.[116] The Supreme Court has candidly acknowledged that "the appropriate methodology for distinguishing questions of fact from questions of law has been, to say the least, elusive."[117] In the absence of a governing principle, we look to the fact/law distinctions drawn by our court in similar cases, practical considerations regarding the allocation of decision-making authority between judge and jury, and the text of *Wyeth* itself. What we discern from these sources is that the question at the heart of the *Wyeth* test—would the FDA have approved the label change plaintiffs argue was required?—is little different from the type of fact questions that are routinely given to a jury.

116 *See Pullman-Standard v. Swint*, 456 U.S. 273, 288, 102 S.Ct. 1781, 72 L.Ed.2d 66 (1982) (the Supreme Court has not devised a "rule or principle that will unerringly distinguish a factual finding from a legal conclusion").

117 *Miller v. Fenton*, 474 U.S. 104, 113, 106 S.Ct. 445, 88 L.Ed.2d 405 (1985).

At root, *Wyeth* requires the decisionmaker to use an existing fact record to predict the outcome of a hypothetical scenario. The question posed to the decisionmaker in this case is: based on the contemporaneous medical literature and the interactions between Merck and the FDA that actually *did* happen, what *would* have happened if Merck had proposed the warning plaintiffs say was required? We think this question is one of fact, for three reasons.

First, we have recognized that an assessment of the probability of a future event should generally be categorized as a finding of fact, even if that finding automatically generates a legal consequence. In *Kaplun v. Attorney General of the United States*,[118] we held that a determination of the probability of future torture was a fact question subject to clear-error review. In so doing, we observed in general terms that "[a] present probability of a future event is something distinct from its legal effect that is made up of facts and actually exists but is not a tangible thing, or actual occurrence."[119] Even though the future event has not occurred, and even if the prediction as to that event's likelihood is dispositive of a legal issue, "the likelihood itself remains a factual finding that can be made *ex ante* the actual outcome." ***290** [120] The *Kaplun* panel cited a number of other non-immigration cases in which we or other circuits have held that inferences drawn from historical facts concerning the likelihood of future events are findings of fact, not law.[121] Here, the corresponding conclusion is that the task of assessing the probability that the FDA would have rejected a particular warning is a factual inquiry rather than a legal one.[122]

118 602 F.3d 260, 269 (3d Cir. 2010).

119 *Id*. at 269 (alterations and internal quotations omitted).

120 *Id*. at 269-70. In other words, the likelihood of an event occurring "is what a decision-maker in an adjudicatory system decides now as part of a factual framework for determining legal effect." *Id*. at 269.

121 *See United States v. Stewart*, 452 F.3d 266, 273 (3d Cir. 2006) (whether the release of an individual creates a

substantial risk of future danger to society is a finding of fact); *Martin v. Cooper Elec. Supply Co*., 940 F.2d 896, 900 (3d Cir. 1991) (inferences from historical facts are factual findings reviewed for clear error); *Onishea v. Hopper*, 171 F.3d 1289, 1300-01 (11th Cir. 1999) (en banc) (district court's finding as to the risk of future prison violence based on conflicting evidence was a factual determination reviewed for clear error).

122 We recognize that the *Wyeth* test is something of an oddity. In a typical case, the historical facts are in dispute and the jury is tasked with figuring out what actually happened. In the case before us, the historical facts are largely undisputed, and the primary disputed fact is the ultimate fact of what *would* have happened. This fact is in turn wholly determinative of the legal question. The law is clear, however, that "an issue does not lose its factual character merely because its resolution is dispositive of the ultimate constitutional question." *Miller*, 474 U.S. at 113, 106 S.Ct. 445. That is the same basic conclusion we reached in *Kaplun*: just because a fact finding completely resolves a legal issue does not alter its fundamentally "factual" character.

Second, *Wyeth* requires the decisionmaker to weigh conflicting evidence and draw inferences from the facts—tasks that the Supreme Court tells us "are jury functions, not those of a judge."[123]

123 *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

The present case is illustrative. Plaintiffs, for their part, rely heavily on the May 2009 letter from Dr. Scott Monroe of the FDA rejecting Merck's proposed warning. According to Plaintiffs, the text of this letter demonstrates that the FDA (or at least Dr. Monroe) objected only to the allegedly misleading term "stress fractures," and does not establish that the FDA was unconvinced of the link between bisphosphonate use and atypical femur fractures. Merck, meanwhile, directs our attention away from Dr. Monroe's letter and instead toward a series of informal FDA communications from the same time period between Dr. Monroe and Merck, which they claim demonstrate that the FDA (or at least Dr. Monroe) was unconvinced of a scientifically-proven link between bisphosphonates and atypical fractures.[124] In short: both sides ask us to (1) draw competing inferences from separate pieces of record evidence and (2) weigh those inferences against one another. These are tasks reserved for jurors, not judges.

124 *See* A 1498, 1971.

Third, the task of predicting the FDA's likely actions requires multiple assessments of FDA officials' motives and thought processes. Consider, for example, some of the questions that must be answered to arrive at a determination of whether the FDA would have rejected Plaintiffs' warning. How convinced or skeptical were FDA officials of the link between bisphosphonates and atypical femur fractures? Even if FDA officials were unconvinced of a firm link, might they nonetheless have agreed that there was "reasonable evidence of a causal association," ***291** as the CBE regulation requires? Did the FDA reject Merck's 2009 proposal because it was unconvinced by the science or because it disliked the stress-fracture language? What, if anything, can we infer from Dr. Monroe's contemporaneous oral statement that the "conflicting nature of the literature" concerning a possible fracture link "does not provide a clear path forward"? Whatever the FDA's position might have been on the association between bisphosphonates and atypical femur fractures, was that position an accurate predictor of its likely response to a proposed warning? In other words, how confidently can we extrapolate FDA officials' hypothetical reactions from their previous statements and actions?

These are all, essentially, inquiries about motive or state of mind: what were FDA officials thinking, and how would that disposition have conditioned their response to plaintiffs' hypothetical proposed warning? And questions of motive, intent, and state of mind are typically understood to be fact questions committed to the jury rather than the court.[125]

125 *See Pullman-Standard*, 456 U.S. at 288, 102 S.Ct. 1781 ("Treating issues of intent as factual matters for the trier of fact is commonplace."); *Monteiro v. City of Elizabeth*, 436 F.3d 397, 405 (3d Cir. 2006) ("Motive is a question of fact that must be decided by the jury"); *Grant v. City of Pittsburgh*, 98 F.3d 116, 125 (3d Cir. 1996) ("[T]he issue of state of mind will always be a question of fact").

One might object that the FDA acts as a body rather than through individuals, thereby rendering questions of "motive" and "intent" irrelevant in this setting.

> The key evidence in this case belies that assumption. At oral argument, Merck's counsel stated that the single best piece of evidence that the FDA would have rejected a revised warning is a set of notes, prepared by a Merck employee, recounting a telephone conversation with Dr. Monroe of the FDA—the same official who wrote the May 2009 letter formally rejecting Merck's proposed additions to the Warnings and Precautions section. According to the employee's notes, Dr. Monroe said that Merck's "elevation of this issue to a precaution in the labeling" was prolonging review, that the "FDA would like to approach the issue of a precaution from the [perspective] of all bisphosphonates," and that because the "conflicting nature of the literature does not provide a clear path forward, ... more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution around these data." A 1971.
>
> To gauge the import of these statements, a decisionmaker would need to, at a minimum, (1) make a credibility determination regarding the Merck employee who drafted the notes; (2) determine the veracity and accuracy of the notes; (3) determine the semantic meaning of Dr. Monroe's statements; (4) infer Dr. Monroe's intent and state of mind when making the statements; and (5) weigh that inference against whatever competing inferences can be drawn from Dr. Monroe's subsequent letter rejecting Merck's proposed warning. These are precisely the types of personal evaluations and weight-of-the-evidence assessments that we commit to jurors in the first instance.
>
> We acknowledge, of course, that the *Wyeth* inquiry may sometimes require the factfinder to impute motive or intent to the FDA as a whole. But as the Supreme Court has recognized, the difficulty of assessing collective intent is not a reason to treat the assessment as something other than a factual inquiry. For example, the Court has held that the question of whether a corporation harbored discriminatory intent is a question of fact. *Pullman-Standard*, 456 U.S. at 289, 102 S.Ct. 1781 ("[D]iscriminatory intent ... is not a question of law and not a mixed question of law and fact."). Here too, the questions of why the FDA took certain actions or what can be inferred from its pronouncements are questions of fact for a jury.

As a fallback position, Merck argues that even if the *Wyeth* inquiry is factual in nature, it should be committed to the court rather than the jury for reasons of institutional competence.[126] Merck relies heavily ***292** on *Markman v. Westview Instruments, Inc.*,[127] in which the Supreme Court held that "construction of a patent, including terms of art within its claim, is exclusively within the province of the court."[128] The *Markman* Court based this conclusion, in part, on the general rule that "[t]he construction of written instruments is one of those things that judges often do and are likely to do better than jurors."[129] Here, the question of how the FDA would have responded to a proposed warning is informed by the regulations that constrain FDA action—in this case, the CBE regulation. That regulation permits the FDA to add an adverse reaction in the Warnings and Precautions section "as soon as there is reasonable evidence of a causal association with a drug."[130] Agency guidance clarifies that "reasonable evidence" is "a standard that could be met by a wide range of evidence," including evidence that "would not also support a higher evidentiary standard, such as a finding that there is a 'preponderance' of evidence that a product actually causes a particular kind of adverse event."[131] Merck therefore claims that application of the clear evidence standard should be left to the courts because it "calls for the interpretation of regulations and agency records freighted with legal meaning."[132]

126 *See Miller*, 474 U.S. at 114, 106 S.Ct. 445 ("[T]he fact/law distinction at times has turned on a determination that, as a matter of the sound administration of justice, one judicial actor is better positioned than another to decide the issue in question.").

127 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996).

128 *Id*. at 372, 116 S.Ct. 1384.

129 *Id*. at 388, 116 S.Ct. 1384.

130 21 C.F.R. § 201.57(c)(6)(i).

131 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008).

132 Merck Supp. Ltr. Br. 4.

This argument misapprehends the nature of the factfinder's task under *Wyeth*. That task is to predict how the FDA would have reacted in a hypothetical scenario. The jury therefore is not being asked to supply a plenary construction of the CBE regulation (or any other written instrument) in the first instance. It is instead being asked to *apply* the requirements of that regulation to the facts, in aid of a prediction as to the FDA's behavior.

The operative language in the CBE regulation is neither uncommon nor abstruse. The "reasonable evidence of a causal association" standard requires law-to-fact applications of the sort that courts routinely give to juries in tort cases. It combines two classic jury questions: (1) whether a causal link between two events is too attenuated, and (2) whether the evidence meets a certain proof threshold. These determinations are well within the province of a properly instructed jury, and we do not think that their inclusion in the larger *Wyeth* inquiry merits reallocation of the factfinding function.

Plaintiffs, meanwhile, argue that judicial decision-making is required when a preemption determination "depends on construction of final, written regulatory actions by the FDA."[133] They further claim that the FDA's May 2009 response letter is just such a "final" document, and urge us to construe it "as a matter of law."[134] We will not go so far. As noted above, it is true that courts are typically charged with determining the construction (*i.e.*, the legal effect) of a writing, as opposed to its interpretation (*i.e.*, the semantic meaning of specific terms). But that general rule has little bearing on the disposition of this case. The question for preemption purposes is whether the FDA would have approved a different label amendment than the one it actually rejected in the ***293** May 2009 letter. The factfinder therefore must parse the FDA's May 2009 letter not to determine its legal effect in the first instance, but rather to discern what it suggests about the FDA's likely response to a differently worded proposal. This too is an appropriate task for the jury.[135]

133 Pls. Supp. Ltr. Br. 3.

134 *Id*. 4.

135 We do not opine on Plaintiffs' contention that the May 2009 letter rejecting Merck's PAS application was a "final regulatory action." If in future cases a court is confronted with a formal regulatory pronouncement that has the force or effect of law, it may be necessary for the court to determine the scope of its legal effect before submitting the ultimate fact question to the jury. A request for such a ruling could be made by motion in limine or at summary judgment. But that exercise is unnecessary here because the immediate "legal" effect of the May 2009 letter, if any, was simply to reject Merck's proposed warning. That limited determination informs but does not answer the larger question of whether the FDA would have approved a differently-worded warning.

> Pivoting to the merits, Plaintiffs direct our attention to an FDA regulation stating that an FDA response letter must "describe all of the specific deficiencies that the agency has identified" in an application. 21 C.F.R. § 314.110(a). Plaintiffs claim that since the May 2009 FDA response letter did not mention any concern over the scientific evidence of a causal association between Fosamax and fractures, we can determine as a matter of law that the FDA would have accepted a proposal that eliminated reference to stress fractures. This is a step too far. Again, the question for the factfinder is whether the FDA would have approved a different warning from the one it rejected. The combination of § 314.110's "complete description" requirement and the FDA's silence in the May 2009 response letter 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. But it does not, and cannot, prove *as a matter of law* that the FDA would have accepted a warning of the type proposed by Plaintiffs.
>
> Nor, for that matter, are we ready to blindly accept Plaintiffs' implicit assumption that Dr. Monroe, the author of the May 2009 letter, followed § 314.110 to a T or had its requirements foremost in mind when drafting. After all, Merck's contention is that Dr. Monroe gave additional reasons for the rejection, not disclosed in the May 2009 letter, in his telephone communications with Merck. We of course do not mean to impugn Dr. Monroe or to suggest that the May 2009 letter did not in fact comply with § 314.110. But the facts of this case demonstrate that we cannot presume the existence of undisputed facts based solely on anticipated compliance with a regulatory rule.

Accordingly, we do not see any convincing prudential reasons to commit the *Wyeth* inquiry to a court rather than a jury. The basic question that *Wyeth* poses to a factfinder—in a counterfactual setting, what do you think the FDA would have done?—requires an evaluative inference about human behavior based on correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and whatever intuitions the factfinder may have about administrative inertia and agency decision-making processes. This assessment is certainly complex, but it does not require any special legal competence or training.

We therefore conclude that the question of whether the FDA would have approved a plaintiff's proposed warning is a question of fact for the jury. A state-law failure-to-warn claim will only be preempted if a jury concludes it is highly probable that the FDA would not have approved a label change.

This decision would change how the preemption defense is presented and utilized in only a subset of cases. As before, drug manufacturers are free to raise a preemption defense, and either party may move for summary judgment on this issue after discovery. Upon summary judgment, district courts will compare the evidence presented with the evidence in *Wyeth*, to determine whether it is more or less compelling. This is in effect what the other ***294** circuits have done. A trial by jury would only be necessary in those cases where the evidence presented is more compelling than that in *Wyeth* but no "smoking gun" rejection letter from the FDA is available. And this need not be at a great expense to either the litigants or the taxpayers. A combined trial may be conducted on both the liability and the defense—similar to patent infringement cases where the plaintiffs present their infringement case at the same time as the defendants present their patent invalidity defense—particularly because the evidence presented will likely overlap. In sum, today's holding will not drastically change how defendants will litigate the preemption defense.

III. ANALYSIS

Having clarified the "clear evidence" standard, we now turn to the merits of Merck's preemption defense.[136]

[136] The District Court had subject matter jurisdiction under 28 U.S.C. § 1332. We have jurisdiction under 28 U.S.C. § 1291.

Plaintiffs' causes of action fall into three groups. The first group comprises Plaintiffs' claims that Merck failed to warn Fosamax users of the risk of atypical femur fractures by failing to add a warning to the Warnings and Precautions section of the label before September 2010 (the "Warnings and Precautions Claims"). The second group comprises Plaintiffs' claims that Merck failed to warn Fosamax users of the risk of femur fractures by failing to add atypical femur fractures to the Adverse Reactions section of the label prior to May 2009 (the "Adverse Reactions Claims"). The third group comprises all of Plaintiffs' non-failure-to-warn claims, including design defect, negligence, breach of implied and express warranties, and violations of state consumer fraud and trade practice statutes (the "Non-Warning Claims"). The District Court ruled that the Warnings and Precautions claims were preempted under *Wyeth*; that the Adverse Reactions claims failed on the merits; and that the Non-Warning Claims were functionally indistinguishable from the Warnings and Precautions Claims and therefore preempted to the same extent.

Plaintiffs present four arguments on appeal. ***First***, Plaintiffs argue that the Warnings and Precautions Claims are not preempted as a matter of law because a reasonable jury could conclude that the FDA would have approved a properly worded atypical-fractures warning. ***Second***, Plaintiffs argue that Merck is not entitled to summary judgment on Plaintiffs' Adverse Reactions Claims because those claims were properly pleaded and there is sufficient evidence for a reasonable jury to find for the Plaintiffs. ***Third***, Plaintiffs argue that even if both sets of failure-to-warn claims are preempted, Plaintiffs' remaining claims are not preempted because they do not "sound in failure to warn" and are supported by competent evidence. ***Fourth***, Plaintiffs claim that the District Court misapplied Rule 56 when it tried to resolve Merck's affirmative preemption defense via a show-cause proceeding.

For the reasons set forth below, we conclude that (1) the Warnings and Precautions claims are not preempted as a matter of law because a reasonable jury could find it less than highly probable that the FDA would have rejected Plaintiffs' proposed warning; (2) Merck is not entitled to summary judgment on the Adverse Reactions claims; and

(3) the Non-Warning Claims are not preempted as a matter of law. Because we are vacating the District Court's summary judgment order, we do ***295** not reach the propriety of the show-cause order.

A. Summary Judgment Standard

[9] [10] [11] [12]Our review of a District Court's grant of summary judgment is plenary,[137] and we affirm only if "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law."[138] Because Merck moved for summary judgment, we must draw all reasonable inferences in the Plaintiffs' favor when considering the evidence.[139] Our inquiry is confined to "whether the evidence of record is such that a reasonable jury could return a verdict for the nonmoving party."[140] We therefore cannot grant summary judgment in Merck's favor "unless a reasonable juror would be compelled to find its way on the facts needed to rule in its favor on the law."[141]

137 *Reedy v. Evanson*, 615 F.3d 197, 210 (3d Cir. 2010).

138 Fed. R. Civ. P. 56(a).

139 *Anderson*, 477 U.S. at 255, 106 S.Ct. 2505.

140 *Reedy*, 615 F.3d at 210.

141 *El v. Se. Pa. Transp. Auth.*, 479 F.3d 232, 238 (3d Cir. 2007).

[13] [14]Special considerations arise in the preemption context. Impossibility preemption is an affirmative defense[142] on which Merck bears the burdens of production and persuasion.[143] Crucially, "the inquiry involved in a ruling on a motion for summary judgment ... necessarily implicates the substantive evidentiary standard of proof that would apply at the trial on the merits."[144] As discussed above, *Wyeth*'s "clear evidence" standard of proof requires the manufacturer to prove that it is highly probable that the FDA would not have approved a change to the drug's label. Therefore, the question for summary judgment purposes is not just whether a reasonable juror could find that the FDA would have approved Plaintiffs' proposed warning. It is whether a reasonable juror could find that it is *highly probable* that the FDA would have rejected the warning. Put differently: even if it seems possible or plausible that the FDA would have rejected the proposed warning, could a reasonable juror nonetheless conclude that the odds of rejection were something less than highly probable? In *El v. Southeastern Pennsylvania Transportation Authority*, we said that "if there is a chance that a reasonable factfinder would not accept a moving party's necessary propositions of fact, pre-trial judgment cannot be granted."[145] The corresponding proposition here is: if there is a chance that a reasonable factfinder would not find that it is highly probable that the FDA would have rejected Plaintiffs' warning, pre-trial judgment cannot be granted.

142 *PLIVA*, 564 U.S. at 634, 131 S.Ct. 2567.

143 *El*, 479 F.3d at 237 & n.6.

144 *Anderson*, 477 U.S. at 252, 106 S.Ct. 2505.

145 *El*, 479 F.3d at 238.

In summary: to affirm the District Court's decision that the Warnings and Precautions Claims are preempted, we must find that no reasonable juror could conclude that it is anything less than highly probable that the FDA would have rejected Plaintiff's proposed atypical-fracture warning had Merck proposed it to the FDA in September 2010.

B. Merck is Not Entitled to Summary Judgment on Plaintiffs' Warnings and Precautions Claims

[15]Merck's ultimate task under *Wyeth* is to prove by clear evidence that ***296** the FDA would not have approved the

warning about the link between Fosamax use and atypical femur fractures that Plaintiffs say was required under state law. Merck's primary argument on appeal is that prior to September 2010, the FDA would have opposed *any* warning about atypical femur fractures in the Warnings and Precautions section because the FDA did not believe that the science supported such a warning. As Merck points out, the FDA sought and analyzed information regarding atypical femur fractures in 2008; Merck responded with data and then proposed warning language for both the Warnings and Precautions and Adverse Reactions sections of the Fosamax label; the FDA rejected Merck's proposed language for the Warnings and Precautions section; and in correspondence surrounding the rejection, FDA officials stated that the "conflicting nature of the literature does not provide a clear path forward," and "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution around these data."[146] Given this sequence of events, Merck argues that there is clear evidence that the FDA would not have approved a CBE submission adding an atypical-fracture warning to the Warnings and Precautions section.

146 A 1971; *see also* A 1498.

It is undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010. In March 2008, Merck submitted a comprehensive safety update to the FDA reporting the existence and results of numerous studies suggesting just such an association. The FDA responded that it was concerned about this "safety signal," but did not require Merck to update its label.[147] In March 2010, after reviewing the data submitted by Merck and other manufacturers, the FDA stated that the data reviewed to date had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."[148] And in October 2010, an FDA Deputy Director stated that the September 2010 task force report was the finding that for the first time made the FDA "confident" that atypical femur fractures are "potentially more closely related to" bisphosphonates "than [the FDA] previously had evidence for."[149] Merck argues that this evidence demonstrates that prior to September 2010, the FDA would have rejected *any* CBE application that attempted to add an atypical fractures warning to the Fosamax label because the FDA had concluded that there was no reasonable evidence of a causal link.

147 A 1935-36.

148 A 1508.

149 A 1396.

Merck also emphasizes the FDA's April 2009 e-mail asking Merck to "hold off on the [Warnings and Precautions] language at this time" so that drug evaluators could "work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide on language for a [Warnings and Precautions] atypical fracture language, *if it is warranted*."[150] After the task force issued its report in September 2010, by contrast, the FDA revised Merck's proposed language and quickly approved a label amendment. Merck argues that the "only logical conclusion from this course of proceedings is that the FDA thought adequate scientific support showing a connection between bisphosphonates and atypical femur fractures was lacking in 2009 but present in 2010 after the [task force] report, ***297** all of which accords with the FDA's public statements on the issue."[151]

150 A 1498 (emphasis added).

151 Merck Br. 50.

Merck also rejects Plaintiffs' theory that the FDA rejected Merck's proposed warning based on a "language quibble" about stress fractures rather than a fundamental disagreement about the science. Merck's strongest argument for summary judgment is that Plaintiffs' theory of the case rests on an unreasonable inference: that the FDA (1) recognized a need to include risk information about atypical femur fractures and therefore would have accepted a properly-worded warning about such fractures, but (2) was so troubled by the "stress fracture" language that it "preferred to deprive physicians of that risk information rather than allow Merck to add its proposed language or authorize inclusion of revised language."[152] Merck buttresses this argument by pointing to statutory

language requiring the FDA to notify a drug manufacturer when it "becomes aware of new safety information that [it] believes should be included in the labeling of the drug" and to "initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information" if it is dissatisfied with the manufacturer's response.[153] Merck points out that if the FDA actually thought that an atypical-fracture warning was warranted, it could have proposed revisions rather than simply rejecting Merck's proposal. The FDA engaged in just such a revision process in 2010 after it directed Merck to add a warning and Merck responded by adding stress-fracture language. The fact that the FDA did not similarly reach out in 2009, Merck says, demonstrates that it would not have accepted Plaintiffs' proposed warning prior to the issuance of the task force report in September 2010.

152 *Id*. 48.

153 21 U.S.C. §§ 355(o)(4)(A) and (C).

We do not discount the force of this evidence or its potential to sway a jury. The problem for Merck, however, is that we are not assessing in the first instance whether there was clear evidence that the FDA would have rejected a change. We are instead trying to anticipate whether a reasonable juror, looking at all the evidence and trying to reconstruct a hypothetical event, could conclude that it is less than highly probable that the FDA would have rejected the change. And crucially for the Plaintiffs, we are drawing all reasonable inferences in their favor. This confers a unique advantage when the factfinder's task is to guess what could have happened in a counterfactual setting.

Plaintiffs' argument against preemption centers on two claims: first, that there was sufficient evidence of a causal link to allow Merck to unilaterally amend the Fosamax label via the CBE process; and second, that the FDA's rejection of Merck's PAS application was based on Merck's misleading use of the term "stress fractures" rather than any fundamental disagreement with the underlying science. In our view, a reasonable jury could accept both contentions and conclude that the FDA would not have rejected Plaintiffs' proposed warning—or, at least, that the FDA was not highly probable to do so.

First, a reasonable jury could conclude that Merck could have amended the Fosamax label via the CBE process. To add a warning to the Warnings and Precautions section of a drug label through a CBE submission, "there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by ***298** a wide range of evidence."[154] To gain FDA approval, therefore, the agency does not need to be affirmatively *convinced* of a causal link between the drug and the adverse event. Here, there is evidence that the FDA recognized a fracture risk and the possible need for warnings before September 2010. In June 2008, for example, the FDA stated that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates," that these and atypical femoral fractures were "reportedly rare in patients with osteoporosis not on bisphosphonates," and that it was "concerned about this developing safety signal."[155] And in May 2009, the FDA approved Merck's request to add a reference to "low energy femoral shaft and subtrochanteric fractures" in the Adverse Reactions section of the label.[156] Even if the FDA did not perceive a "clear connection" between Fosamax and atypical fractures, as it said in early 2010, a juror could conclude that the FDA would still have determined that "reasonable evidence" of a link existed—or more precisely, that the possibility of rejection was less than highly probable.

154 73 Fed. Reg. at 49,604. The same "reasonable evidence" standard that governs whether a manufacturer can submit a CBE application also governs whether the FDA should approve it. 21 C.F.R. § 201.57(c)(6)(i).

155 A 1145.

156 A 1500-01. As Plaintiffs point out, warnings can only be added to the Adverse Reactions section if they are "reasonably associated with use of" a drug and "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7) (FDA regulation describing requirements of "Adverse Reactions" section of label). A juror could therefore infer from the FDA's approval of the Adverse Reactions language that the FDA would have also agreed that there was "reasonable evidence of a causal association" between

Fosamax and atypical femoral fractures.

Second, a reasonable jury could also conclude that the FDA rejected Merck's proposed warning about femoral fractures in 2009 not because it denied the existence of a causal link between Fosamax and fractures, but because Merck repeatedly characterized the fractures at issue as "stress fractures." Merck's proposed warning used the phrase "stress fractures" six times.[157] According to Plaintiffs' expert, stress fractures are commonly seen in physically active people; atypical femoral fractures are, as the name suggests, highly unusual.[158] Stress fractures are usually incomplete ***299** fractures that heal with rest, while atypical femoral fractures often are complete fractures that require surgical intervention.[159] The FDA's response to Merck's PAS application stated: "Your justification for the proposed PRECAUTIONS section language is inadequate. Identification of 'stress fractures' may not be clearly related to the atypical subtrochanteric features 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."[160] The FDA did not give any other reason for rejecting Merck's proposed warning.

157 The following is the text of Merck's proposed addition to the Warnings and Precautions section, with references to "stress fractures" bolded:

> Low-Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. **Some were stress fractures** (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, **often associated with imaging features of stress fracture**, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and **stress fractures with similar clinical features also have occurred** in patients not treated with bisphosphonates. **Patients with suspected stress fractures** should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in **patients with stress fractures** should be considered, pending evaluation of the patient, based on individual benefit/risk assessment. A 2720.

158 A 868 ¶ 22; A 881 ¶ 74; A 882 ¶ 76; *see also* A 1147 (task force report describing atypical femoral fractures as occurring with "relative rarity").

159 A 884 ¶ 83-84; *see also* A 1149 (task force report describing atypical femoral fractures as "[c]omplete fractures").

160 A 1500-01.

In 2010, when Merck attempted to revise the FDA's proposed warning by adding references to stress fractures, the FDA again struck out the stress-fracture references. It 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."[161]

161 A1540.

As discussed above, Merck argues that if the FDA had been truly concerned about the risk of atypical fractures, it could have revised and approved a warning without the offending stress-fracture references. As a matter of law, however, the burden and the responsibility to correct a drug label rests with the manufacturer, not the FDA.[162] Once the FDA rejected Merck's proposal, the ball was back in Merck's court to submit a revised, corrected proposal. A reasonable juror could therefore conclude 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.

162 *See Wyeth*, 555 U.S. at 570-71, 129 S.Ct. 1187 ("[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of

federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."); 21 U.S.C. § 355(o)(4)(I) ("Rule of construction" clarifying that the 2007 FDCA amendments "shall not be construed to affect the responsibility of the responsible person ... to maintain its label in accordance with existing requirements").

Plaintiffs' evidence certainly does not *compel* the conclusion that the FDA would have accepted an atypical fracture warning that omitted the language about stress fractures. But our inquiry at this stage is not about who has the best evidence; it is about what a reasonable jury applying a heightened standard of proof *could* conclude on the basis of the evidence. Because the *Wyeth* test requires the factfinder to speculate about hypothetical scenarios using inferences drawn from historical facts, reasonable jurors could reach a broad range of conclusions when confronted with this record. To that inherent uncertainty we then add all the reasonable inferences that Rule 56 requires us to draw in Plaintiffs' favor: the FDA would have agreed that the evidence of an association was "reasonable" prior to 2010; the FDA rejected Merck's proposed warning because it was primarily concerned with the misleading references to stress fractures rather than the underlying science; the FDA refrained from counter-proposing an acceptable warning in 2009 because it considered it Merck's responsibility to submit a ***300** revised warning; the FDA affirmatively reached out to Merck in 2010 because it recognized that the science was now so strong that amending the label was a legal imperative, not because it was acknowledging a sufficient risk for the first time.

A reasonable juror reviewing the evidence in this case could find it less than highly probable that the FDA would not have approved a warning about the risk of atypical femur fractures that eliminated or revised references to "stress fractures." Accordingly, Merck is not entitled to summary judgment on its preemption defense to Plaintiffs' Warnings and Precautions claims.[163]

163 Our ruling today concerns only the correctness of the District Court's March 24, 2014 decision that Merck was entitled to summary judgment on its affirmative preemption defense. We express no view as to whether or how our ruling should be applied to any individual action in the MDL going forward.

One of the reasons Merck gave for treating *Wyeth* preemption as a pure question of law was that doing so would allegedly ensure consistency of its application across the hundreds of claims in this MDL. We of course do not decide issues by considering how many lawsuits our ruling will extinguish or revive. At any rate, the suits in this MDL pose numerous binary jury questions that conceivably apply across the board. Fosamax either causes atypical femoral fractures or it does not; Merck either knew about the alleged risks of fracture or it did not; the risks of Fosamax either outweighed its benefits or they did not; the list goes on. Ontologically speaking, there is an "objective" right answer to each of these questions that does not vary from case to case. And treating each issue as one of pure law to be disposed at a swoop of the judge's pen would certainly speed matters along. But neither consideration is an adequate basis to shift the traditional line between judge and jury functions. Of course, if the manufacturer shows that there is no genuine dispute as to any material fact bearing on *Wyeth* preemption, then a judge can indeed decide as a matter of law that the defense is established. But that showing was not made here. The FDA either would have approved Plaintiffs' warning or they would not; we cannot say.

Treating preemption as a jury issue does not automatically condemn Merck to a thousand individual jury trials. The MDL parties could, for example, hold a bellwether trial on the preemption question, after which the prevailing party would be free to argue that the other side should be collaterally estopped from re-litigating preemption in individual cases. *See Markman*, 517 U.S. at 391, 116 S.Ct. 1384 (recognizing that treating a question as a factual issue does not leave it "wide open in every new court" because "principles of issue preclusion would ordinarily foster uniformity"). Again, we express no view on the merits or likely outcomes of such an approach.

C. Merck is Not Entitled to Summary Judgment on Plaintiffs' Adverse Reactions Claims

Plaintiffs' failure-to-warn claims focus primarily on the assertion that Merck should have added a fractures warning to the Warnings and Precautions section of the Fosamax label prior to September 2010. But Plaintiffs also contend that their failure-to-warn claims encompass a related but distinct allegation that Merck should have added atypical fractures to the Adverse Reactions section prior to May 2009 (the date the FDA actually approved

Merck's addition of atypical fractures to the Adverse Reactions section), and that Merck's failure to do so proximately caused their injuries.[164] The District Court ruled that this claim was insufficiently pled and not supported by the evidence, and entered summary judgment for Merck on the merits. This ruling was in error.

164 *See* A 1501.

As an initial matter, the Adverse Reaction Claims are not preempted by *Wyeth*, and Merck does not argue otherwise. Merck requested that atypical fractures be added to the Adverse Reactions section in 2009, and the FDA approved the request. Merck has not shown by clear evidence ***301** that the FDA would have rejected such a warning had Merck proposed it earlier.

Turning to the merits, the District Court dismissed the Adverse Reactions claims on two grounds.[165] The first basis for the District Court's ruling was its conclusion that Plaintiffs did not specifically plead a failure-to-warn claim based on the Adverse Reactions label section in any of their complaints. Whether or not this is an accurate assessment—we do not have every MDL complaint before us to confirm, and there is no indication that the District Court reviewed each of the hundreds of complaints at issue either—we think it beside the point. Plaintiffs direct us to a number of complaints alleging generally that the Fosamax label did not adequately warn patients and doctors of the fracture risk, without specifying the particular warnings that should have been included or the particular failings of each label section.[166] The parties and the District Court all accept that these general allegations adequately pled the Warnings and Precautions theory discussed above. It is therefore difficult to understand why the District Court faulted the same complaints for failing to specify every section of the label that should have included a warning. At any rate, such specificity is not required by the Federal Rules of Civil Procedure.[167] Merck does not argue that the complaints failed to put it on notice of the Adverse Reactions claim, and that concession closes the door on any claim that the complaints themselves failed to adequately plead the Adverse Reactions theory.

165 Although it does not appear to have been a basis for its decision, the District Court observed that a large number of Plaintiffs alleged injuries occurring after the FDA added the Adverse Reactions warning. According to the District Court, these Plaintiffs would only be able to assert a failure-to-warn claim based on the absence of a warning in the Warnings and Precautions section of the label. We disagree, as these Plaintiffs remain free to argue that their injuries were caused by their *use* of Fosamax prior to the addition of the Adverse Reactions warning.

166 *See* A 2245 ¶ 54, 2249 ¶ 76, 2190 ¶ 123, 2333 ¶ 57.

167 *See Oneida Indian Nation v. Cty. of Oneida*, 617 F.3d 114, 132 (2d Cir. 2010) (complaint need not specify the legal theory underlying its claims so long as it contains sufficient facts to support liability); *Kirksey v. R.J. Reynolds Tobacco Co.*, 168 F.3d 1039, 1041 (7th Cir. 1999) (same).

[16]The District Court also stated, without elaboration, that Plaintiffs had failed to "set forth evidence indicating that any doctor would not have prescribed Fosamax if the occurrence of low-energy femoral shaft fractures had been mentioned in the Adverse Reactions section prior to 2009."[168] Even if true, this does not justify summary judgment on the merits. The proper inquiry for summary judgment purposes is whether there was sufficient evidence to permit a reasonable juror to conclude that a doctor would not have prescribed Fosamax if fracture language had been added to the Adverse Reactions section prior to 2009. To this end, Plaintiffs submitted several declarations from their treating physicians declaring that if they had been informed that Fosamax posed a risk of femoral fractures, they likely would not have prescribed Fosamax or likely would have discontinued treatment.[169] These declarations do not specify which sections of the label should have contained such a warning. A reasonable juror could conclude that some of these physicians would not have prescribed Fosamax if ***302** atypical femur fractures had been listed in the Adverse Reactions section. Accordingly, the District Court should not have granted Merck summary judgment on the merits of Plaintiffs' Adverse Reactions failure-to-warn claims.

168 *Summary Judgment Order*, 2014 WL 1266994, at *15.

169 *See, e.g.*, A 792 ¶ 10, 794 ¶ 9, 796-97 ¶ 9, 798 ¶ 8.

[17]There is a deeper problem lurking in the District Court's decision to grant Merck a merits judgment in all of the MDL cases. A mass tort MDL is not a class action. It is a collection of separate lawsuits that are coordinated for pretrial proceedings—and *only* pretrial proceedings—before being remanded to their respective transferor courts.[170] Some purely legal issues may apply in every case. But merits questions that are predicated on the existence or nonexistence of historical facts unique to each Plaintiff—*e.g.*, whether a particular Plaintiff's doctor would have read a warning in the Adverse Reactions section and ceased prescribing Fosamax as a result—generally are not amenable to across-the-board resolution. Each Plaintiff deserves the opportunity to develop those sort of facts separately, and the District Court's understandable desire to streamline proceedings cannot override the Plaintiffs' basic trial rights.[171] As a technical matter, Merck's *actual* burden at the summary judgment stage was to prove that there is no genuine dispute in *every single MDL case* that Plaintiffs' doctors would have continued to prescribe Fosamax even if the fracture warning had been added to the Adverse Reactions section before May 2009. It could not do so, and the District Court's grant of summary judgment on the merits was therefore erroneous.

170 28 U.S.C. § 1407(a).

171 The District Court and the parties could have, but did not, choose to have the Plaintiffs assemble a single "master complaint" that superseded the individual complaints. *See In re Refrigerant Compressors Antitrust Litig.*, 731 F.3d 586, 590-91 (6th Cir. 2013).

D. Merck is Not Entitled to Summary Judgment on Plaintiffs' Non-Warning Claims

[18]The District Court held that Plaintiffs' Non-Warning Claims sounded in failure to warn and were therefore preempted to the same extent as the Warning and Precautions Claims. Accordingly, our decision vacating the District Court's preemption ruling as to the Warnings and Precautions Claims reinstates the Non-Warning Claims as well.[172] We pass no judgment on the merits of those claims or on whether they do in fact sound in failure to warn.

172 Merck argues that the non-warning claims are separately preempted by the Supreme Court's decision in *Mutual Pharmaceutical Co. v. Bartlett*, —— U.S. ——–, 133 S.Ct. 2466, 186 L.Ed.2d 607 (2013). Merck admits, however, that it did not raise this argument below—indeed, Merck appears to have explicitly disavowed the argument so it could characterize its defense as being based solely on *Wyeth*. Merck Br. 68; A 1727-28. "It is well established that arguments not raised before the District Court are waived on appeal." *DIRECTV Inc. v. Seijas*, 508 F.3d 123, 125 n.1 (3d Cir. 2007). We see no reason to deviate from that rule here.

IV. CONCLUSION

For the foregoing reasons, we will vacate the District Court's grant of summary judgment to Merck and remand for further proceedings consistent with this opinion.

Appendix A

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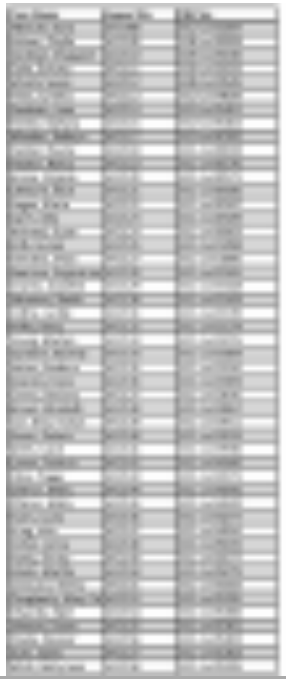

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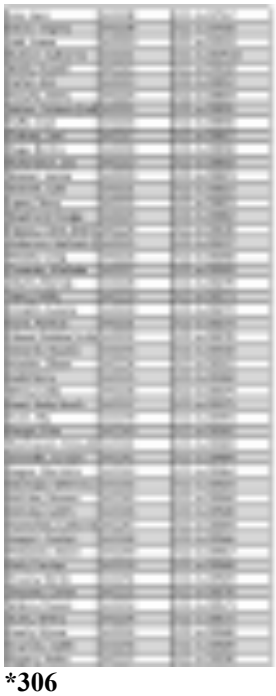

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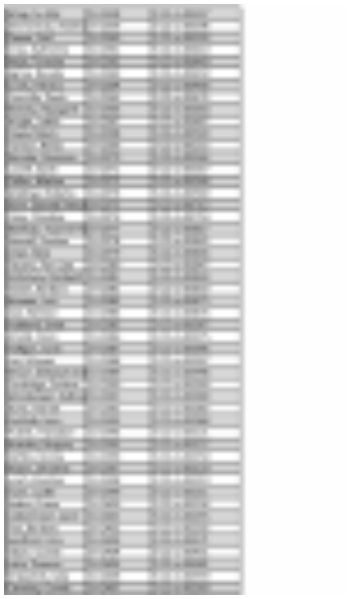

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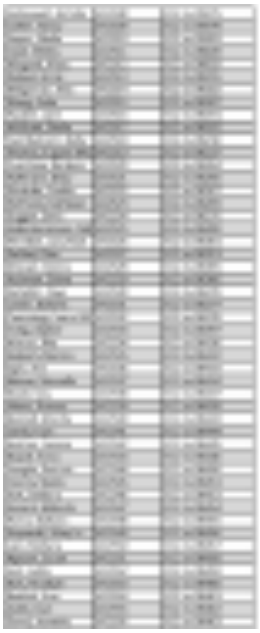

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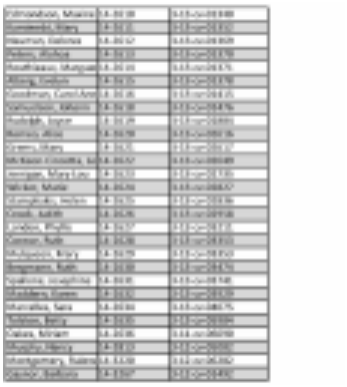

All Citations

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