No. 16-4050

IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

ALEXANDER CERVENY, VICTORIA CERVENY,
AND CHARLES CERVENY
Plaintiffs/Appellants

v.

AVENTIS, INC.,
Defendant/Appellee

Appeal from the United States District Court for the District of Utah
Case No. 2:14-CV-00545
The Honorable Dee Benson, United States District Judge

Brief of Chamber of Commerce of the United States of America, American Tort Reform Association, and National Association of Manufacturers as Amici Curiae in Support of Appellee Aventis, Inc.

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, disclosure is hereby made by *amici curiae* Chamber of Commerce of the United States of America; American Tort Reform Association; and National Association of Manufacturers, of the following corporate interests:

a. Parent companies of the corporation:

None.

b. Any publicly-held company that owns ten percent (10%) or more of the corporation:

None.

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GLOSSARY

CBE ..... FDA's Changes Being Effected Regulation

FDA ..... United States Food & Drug Administration

FDCA..... Federal Food, Drug & Cosmetic Act

PAS..... FDA's Prior Approval Supplement Regulation

INTEREST OF *AMICI CURIAE*[1]

The Chamber of Commerce of the United States of America ("the Chamber") is the world's largest not-for-profit business federation. For more than 100 years, it has represented American businesses of every size, in every sector of the economy, and from every region of this country. The Chamber represents 300,000 direct members and indirectly represents the interests of three million businesses and trade and professional organizations. An important function of the Chamber is to represent the interests of its members in matters before Congress, the Executive Branch, and the courts. To that end, the Chamber regularly files *amicus* briefs in cases that raise issues of concern to the nation's business community.

The American Tort Reform Association ("ATRA") is a broad-based coalition of businesses, municipalities, associations, and professional firms that have pooled their resources to promote reform of America's civil justice system. The members of ATRA share the goal of ensuring

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

fairness, balance, and predictability in civil litigation. For more than two decades, ATRA has filed *amicus* briefs in cases before state and federal courts that have addressed important liability issues.

The National Association of Manufacturers ("NAM") is the largest manufacturing association in the United States, representing small and large manufacturers in every industrial sector and in all 50 States. Manufacturing employs more than 12 million men and women, contributes roughly $2.1 trillion annually to the American economy, has the largest economic impact of any major sector, and accounts for three-quarters of private-sector research and development. The NAM is the powerful voice of the manufacturing community and the leading advocate for a policy agenda that helps manufacturers compete in the global economy and create jobs across the United States.

The Chamber, ATRA, and NAM are participating as *amici* because failure-to-warn claims against manufacturers stuck between federal and state law impose unfair and inefficient costs on businesses and, as a result, on the public. Where federal law does not authorize a drug manufacturer to change its warning label in the way that state law allegedly requires, a failure-to-warn claim is preempted. Plaintiffs-

appellants' contrary position "would render conflict pre-emption largely meaningless." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011).

INTRODUCTION AND SUMMARY OF THE ARGUMENT

The Food, Drug & Cosmetic Act requires brand-name drug manufacturers to use the exact warning label approved by FDA as part of its approval of the drug. FDA has created a narrow regulatory exception to that statutory rule—its Changes Being Effected, or CBE, regulation, which authorizes manufacturers to make certain changes unilaterally and without advance FDA approval (though FDA retains the authority to reject the change after it has been effected).

The CBE regulation does not authorize manufacturers to make whatever changes they want or whatever changes a plaintiff may contend that state law requires. To the contrary, it permits only a narrow subset of changes, with both temporal and substantive limitations on the information that can justify a CBE change. First, a manufacturer may invoke the CBE regulation only based on new information not previously submitted to FDA; otherwise, a CBE change could simply reverse FDA's decision about what the label should say. Second, the regulation applies only where the new information rises to

the level of constituting "reasonable evidence of a causal association" with a hazard; otherwise, scientifically unwarranted overwarning could deter patients from taking safe and effective drugs.

The Supreme Court relied heavily on the existence of the CBE regulation in holding, in *Wyeth v. Levine*, 555 U.S. 555, 568-69 (2009), that state-law failure-to-warn claims were not generally preempted by FDA approval of a drug's label. And it was precisely because the CBE regulation is unavailable to generic drug manufacturers that the Court reached the opposite result in *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011).

Mensing clarified that the preemption inquiry asks whether the manufacturer could have made the label change supposedly required by state law "independently" and "under federal law." *Id.* at 620. FDA's CBE regulation is the only mechanism under federal law for a manufacturer to make a unilateral change to a drug's warning label without obtaining advance approval from FDA. Because that mechanism is not available to generic manufacturers, failure-to-warn claims against them are preempted. For brand-name manufacturers, whether the CBE regulation authorized them to make a label change

supposedly required by state law depends on whether the label change met the CBE regulation's standards—*i.e.*, whether that change was justified by newly-acquired information rising to the level of reasonable evidence of a causal association with a hazard.

Plaintiffs' brief ignores the legal standards contained in the CBE regulation. According to plaintiffs, preemption should apply only if the manufacturer changed its label in the way that state law required and FDA then rejected the change; in any other scenario, plaintiffs contend, it inevitably is too uncertain whether FDA would have rejected a label change. *See* Pl. Br. 27. Where a manufacturer changes its label and FDA orders it to change it back, that is of course powerful proof that the CBE regulation did not authorize the change. And FDA's rejection of the label change advocated by plaintiffs in its denial of Mr. Mix's citizen petition is no less powerful proof, given that the same legal standard applied to FDA's decision on the citizen petition as would have applied had Aventis proposed the change. There is no need to consider what FDA *would have done* where FDA *in fact* rejected the label change at issue.

But more fundamentally, asking what FDA would have done in a counterfactual scenario had the manufacturer made a particular change misses the point. Preemption turns on a *legal* question—whether the CBE regulation authorized the manufacturer to make the change—not on how FDA might have exercised its enforcement discretion had the manufacturer made a change that the CBE regulation did not authorize. Put differently, preemption turns on whether the manufacturer could have made the change allegedly required by state law independently and in compliance with federal law—not on whether the manufacturer might have gotten away with it had it made the change in violation of federal law.

As explained in the district court's thorough opinion and in Aventis's brief, the answer to the controlling legal question here is clear: There was no valid basis in federal law for Aventis to make the label change that plaintiffs contend state law required, because the information available did not rise to the level of reasonable evidence of a causal association with the hazard at issue. FDA itself explained as much at length in denying Mr. Mix's citizen petition advocating that change. That FDA made that decision in denying a citizen petition

rather than in countermanding an unauthorized CBE change hardly defeats preemption. The critical point is that making that change through the CBE process would not have been authorized by federal law. That would be equally true even if FDA had never had occasion to address the issue; the fact that FDA decided the precise issue at hand simply makes the preemption question here an easy one.

ARGUMENT

I. Courts Assessing Conflict Preemption Must Ask Whether Federal Law Authorized The Defendant To Do What The Plaintiff Claims State Law Required.

A. Federal Law Preempts State-Law Failure-To-Warn Claims Where A Manufacturer Cannot—Independently And In Accordance With Federal Law—Do What State Law Requires.

The Supremacy Clause bars a state-law claim, under what is often called "conflict preemption," where it is "impossible for a private party to comply with both state and federal requirements." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990). In its 2011 decision in *Mensing*, the Supreme Court specifically addressed what "impossibility" means in the context of claims that a drug's FDA-approved warning label was inadequate under state law, holding that the "question for

'impossibility' is whether the private party could independently do under federal law what state law requires." *Mensing*, 564 U.S. at 620.

The Court further clarified what it means for a manufacturer to be able to "independently" comply with both state and federal law: the manufacturer must have been able to make a "unilateral change" to its label to provide the warning allegedly required by state law. *Id.*; *see also Mutual Pharm. Co., Inc. v. Bartlett,* 133 S. Ct. 2466, 2475 (2013); *Wyeth*, 555 U.S. at 573. Accordingly, in *Mensing* it did not matter whether the defendants, manufacturers of generic drugs, could have taken steps in the direction of what state law allegedly required by "ask[ing] the FDA for assistance in changing their labels"; what mattered was that they did not have the right under federal law to change the labels by themselves. 564 U.S. at 619-21 (dismissing plaintiffs' argument that manufacturers "did not even *try* to start the process that might ultimately have allowed them to use a safer label").

The Court also clarified that the preemption analysis looks to whether the manufacturer was capable of complying with state law while also acting "under federal law" based on what federal law permitted at the time, not with regard to what it "might eventually

have been able to accomplish under federal law." *Id.* at 618-19. Thus, the possibility that federal law might have changed—or even that the manufacturer might have been able to induce a change in federal law—is beside the point. *Id.* at 621 ("[I]t is also *possible* that, by asking, the Manufacturers could have persuaded the FDA to rewrite its generic drug regulations entirely or talked Congress into amending the Hatch-Waxman Amendments."). Such conjecture fails to look to the governing, federal legal standard and "renders conflict pre-emption all but meaningless." *Id.* In short, under *Mensing* the preemption inquiry asks whether, at the time relevant to plaintiffs' claims, federal law authorized Aventis to unilaterally change its drug's FDA-approved warning label in the way that state law supposedly required.

Before *Mensing*, in its first case to discuss preemption of state-law failure-to-warn claims against a pharmaceutical manufacturer, the Supreme Court had relied heavily on the existence of FDA's CBE regulation, which permits manufacturers to make unilateral changes to warning labels under certain circumstances. *Wyeth*, 555 U.S. at 570-71, 573. In *Wyeth*, the Court found "'no evidence in th[e] record that either the FDA or the manufacturer gave more than passing attention to the

issue'" underlying the state-law claim and concluded that the manufacturer "failed to demonstrate that it was impossible for it to comply with both federal and state requirements" by using the CBE process. *Id.* at 572. The Court thus found preemption inapplicable in that case, while commenting that "clear evidence that the FDA would not have approved a change to [the] label" would establish preemption. *Id.* at 571.

In the immediate wake of *Wyeth*, lower courts struggled with how to interpret the Court's reference to "clear evidence." Just two years later, however, the Court clarified matters in *Mensing*. Consistent with *Wyeth*'s holding that state-law failure-to-warn claims are not preempted where the manufacturer could have used the CBE process to make the label change allegedly required by state law, *Mensing* clarified that claims *are* preempted where the manufacturer could *not* have done so consistent with federal law. Thus, the key question becomes whether federal law permitted the manufacturer to make the plaintiff's proposed label change under the CBE regulation.

The precise issue in *Mensing* was whether failure-to-warn claims against generic manufacturers were preempted by federal law's

requirement that generic manufacturers maintain the same labeling as the brand-name reference drug. 564 U.S. at 612. The plaintiffs argued that the CBE regulation, relied upon by the *Wyeth* Court in analyzing preemption as to brand-name manufacturers, was equally open to generic drug manufacturers. The Court, however, deferred to FDA's view that its CBE regulation was open to generic manufacturers "only when a generic drug manufacturer changes its label to match an updated brand-name label or to follow the FDA's instructions." *Id.* at 614. Because "the CBE process was not open" to the generic manufacturers to strengthen their warning labels on their own initiative as the plaintiffs contended state law required, it was impossible for the manufacturers to comply with both state and federal law. *Id.* at 615. As the First Circuit explained in the leading post-*Mensing* appellate decision, "[t]he [*Mensing*] Court thus limited *Wyeth* to situations in which the drug manufacturer can, 'of its own volition, … strengthen its label in compliance with its state tort duty.'" *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41 (1st Cir. 2015) (citing *Mensing*, 564 U.S. at 624).[2]

[2] *Mensing* thus abrogated post-*Wyeth* decisions that rejected preemption

Two years later, the Court reaffirmed *Mensing*'s approach in *Mutual Pharmaceutical Company, Inc. v. Bartlett*. In *Bartlett*, as in *Mensing*, federal law did not authorize the manufacturers to make the label change that the plaintiffs said state law required, but the plaintiffs nonetheless argued that preemption was inapplicable because the manufacturers could have complied with both state and federal law either by ceasing to sell the drug in the state at issue or by continuing to do so, in alleged violation of state law, and paying the state-law liability thereby incurred.

The Court rejected this argument, focusing once again on what the law required and explaining that plaintiffs could "not turn impossibility into possibility" by suggesting that a defendant solve the dilemma of inconsistent federal- and state-law requirements by complying with federal law and suffering the state-law consequences. *Bartlett,* 133 S. Ct. at 2477 & n.3. Whether or not it was "'literally impossible'" to comply with both state and federal law, *id.*, the "Court reasoned that

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based on the manufacturer's potential ability to press FDA to allow a label change that was not legally authorized under the CBE regulation. *See, e.g.*, *Aaron v. Wyeth*, No. 07-cv-927, 2010 WL 653984, at *6 (W.D. Pa. Feb. 19, 2010) (hypothesizing that FDA, even after rejecting the proposed label change, might eventually have done something different if the manufacturer had "press[ed] its position").

'an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability.' 'To hold otherwise would render impossibility preemption all but meaningless.'" *In re Celexa*, 779 F.3d at 41-42 (citing *Bartlett*, 133 S. Ct. at 2477 & n.3)).

Although *Mensing* and *Bartlett* involved generic, not brand-name, manufacturers, the Court's holdings about what constitutes "impossibility" and how conflict preemption works are of course not limited to generic manufacturers or even to the pharmaceutical context. Indeed, in *Bartlett*, the Court discussed the restrictions imposed by federal law "[o]nce a drug—*whether generic or brand-name*—is approved." 133 S. Ct. at 2471 (emphasis added). As explained in more detail below, *see infra* Section II.A-B, the Federal Food, Drug, and Cosmetic Act ("FDCA") prohibits brand-name and generic manufacturers alike "from making any unilateral changes to a drug's label," but FDA has created a limited regulatory exception—its CBE regulation. *See Bartlett*, 133 S. Ct. at 2471. Because the CBE regulation is not available to generic manufacturers, the statutory prohibition applies to them, full stop. As to brand-name manufacturers, the

prohibition applies to them except to the extent that the CBE regulation authorizes a label change. *See, e.g.*, *Mensing*, 564 U.S. at 614-15 (discussing when CBE process is "open" to manufacturers under federal law).

The district court in this case hewed closely to *Wyeth*'s language concerning whether FDA would have rejected plaintiffs' proposed label change, and Aventis's brief explains why it is clear—even taking that language on its own terms—that FDA would have done so (and in fact *did* so). *Amici* believe, however, that that language in *Wyeth* must be read in the light shed by *Mensing* and *Bartlett*. Following the Court's clarifications of the impossibility inquiry in those cases, courts have recognized that *Wyeth*'s language concerning whether FDA would have rejected a label change is really a reference to what the Court in *Mensing* held is the "question for impossibility"—namely, whether a label change would have satisfied the CBE regulation's legal standards. If the CBE regulation does not authorize the manufacturer to make a given change, the manufacturer cannot "independently do under federal law what state law requires" and preemption applies. 564 U.S. at 620.

For example, faced with a state-law claim that an FDA-approved label was misleading because it omitted certain information, the First Circuit focused on whether the CBE regulation authorized the manufacturer to make the label change allegedly required by state law. The court explained that the Supreme Court's preemption decisions "make[] clear that a necessary step in defeating [a manufacturer's] preemption defense is to establish that the complaint alleges a labeling deficiency that [the manufacturer] could have corrected using the CBE regulation." *In re Celexa*, 779 F.3d at 41. Because the information relied upon by the *Celexa* plaintiffs was not new, it did not fall within the CBE regulation's limited authorization for a unilateral label change. *See id.* at 42-43. And because federal law thus did not "*allow*[] [the manufacturer] to use the CBE procedure to alter the FDA label in the manner that plaintiffs" contended state law required, the First Circuit held that the claims were preempted. *Id.* at 43; *see id.* at 35 (holding that "federal law impliedly preempts these claims because the [FDCA] prohibits [manufacturer] Forest from independently changing its FDA-approved label as plaintiffs claim California law requires").

B. Plaintiffs Ask The Court To Ignore Whether A Manufacturer Can Independently And Lawfully Change Its FDA-Approved Label.

Rather than looking to whether federal law authorized Aventis to make the label change they say state law required, plaintiffs ignore the CBE regulation's legal standards and hypothesize about what FDA might have done had Aventis submitted a CBE supplement making that change. Thus, plaintiffs ask this Court to answer the wrong question, arguing (Br. 12) that "the fact that the FDA did not **force** Aventis to change its label after a single citizen requested such action does not conclusively reveal how the FDA would have responded, had Aventis changed its label unilaterally."

Perhaps plaintiffs' error stems from their mistaken assumption that brand-name manufacturers are always free to invoke the CBE regulation to add or strengthen a warning regardless of the scientific support or lack thereof for the change. *See* Pl. Br. 15 (asserting that "manufacturers can universally change their labels to add safety warnings, through the Changes Being Effected ("CBE") process"). Or perhaps plaintiffs believe that it does not matter whether federal law authorized Aventis to make the label change they say state law

required and are pinning their hopes on the hypothesis that FDA might have let an unauthorized change stand, whether as a matter of enforcement discretion or simple bureaucratic inertia. *See* Pl. Br. 33, 38.

Either way, plaintiffs' error is clear. As explained above, the Supreme Court's most recent and on-point precedents instruct the Court to decide whether Aventis would have been *authorized* to make plaintiffs' proposed label change via a CBE supplement. *See In re Celexa*, 779 F.3d at 41 (preemption turns on "whether the CBE regulation allows a brand name manufacturer to make the particular type of change that plaintiffs say [the manufacturer] needed to have made to avoid liability under [state] law"). The FDCA and FDA regulations authorize a manufacturer to add or strengthen a warning via the CBE process only where the change meets the criteria set forth in the CBE regulation, including in particular that there must be reasonable evidence of a causal association between the drug and new risks based on newly-acquired information. *See infra* Section II.B. In assessing whether to make a unilateral change to its FDA-approved label via the CBE pathway, a manufacturer must evaluate whether the contemplated change meets the regulatory standards *before* making the

change. Plaintiffs assert that "FDA is infinitely more likely to grant a manufacturer's application to change a label than a citizen petition asking the FDA to require a label change," Br. 36, but if that proposition is true, it is only because manufacturers understand the regulatory standards and endeavor to comply with them.

Plaintiffs suggest that FDA does not really apply the standards that its regulations require, but they offer no evidence that this is true. And certainly the Court should not assume that it is. *See, e.g.*, *Blinder, Robinson & Co., Inc. v. U.S. S.E.C.*, 748 F.2d 1415, 1418 (10th Cir. 1984) ("It is presumed that administrative agencies . . . will act within the law." (citing *F.C.C. v. Schreiber*, 381 U.S. 279, 296 (1965))). But in any case, impossibility does not hinge on what FDA might have done. *Cf. Mensing*, 564 U.S. at 621 ("If these conjectures suffice . . . it is unclear when, outside of express pre-emption, the Supremacy Clause would have any force."). What matters is the legal standard FDA has established in its CBE regulation and whether Aventis could have made the changes plaintiffs demand while complying with that standard. And to whatever extent what FDA *would have done* is relevant, that question can be answered only by asking whether the legal standard

FDA has prescribed *would have authorized the change*. It would be improper for courts to assume that FDA would have done anything other than faithfully apply its own regulations.

Moreover, even apart from their disregard of *Mensing*'s explanation of what impossibility means in this context, plaintiffs disregard the language of *Wyeth* itself. Plaintiffs would limit preemption to cases where FDA *in fact rejected* a manufacturer's label change. But even *Wyeth* recognized that preemption would apply if it were clear that FDA "*would not have approved*" the label change allegedly required by state law. *See Wyeth*, 555 U.S. at 571 (emphasis added); *see also, e.g.*, *Seufert v. Merck Sharp & Dohme Corp.*, No. 13cv2169, 2016 WL 3369512, at *5 (S.D. Cal. May 11, 2016) (noting that *Wyeth*'s language "necessarily considers instances where a manufacturer has not submitted a labeling change to the FDA"), *appeal pending*, No. 16-55853 (9th Cir.); *In re Incretin-Based Therapies Prod. Liab. Litig.*, 142 F. Supp. 3d 1108, 1126 (S.D. Cal. 2015) ("the Court finds … that [*Wyeth v.*] *Levine* does not require CBE submission and rejection"). Plaintiffs' contention that "'clear evidence' should never be found in the absence of an effort by the manufacturer to change the

label that the FDA rejected," Br. 24, mistakes a sufficient condition for a necessary one.

II. Federal Law Authorizes a Drug Manufacturer To Change its FDA-Approved Label Only In Limited Circumstances.

A. The FDCA and FDA Regulations Ordinarily Require A Manufacturer To Obtain FDA Approval Before Altering a Drug's Label.

Most prescription drugs (including Clomid) are considered "new drugs" within the meaning of 21 U.S.C. § 321(p) and therefore may not be sold without FDA approval. To obtain approval, a manufacturer must submit a New Drug Application, which includes, *inter alia*, evidence establishing "whether or not such drug is safe for use and whether such drug is effective in use" under the conditions of use described in its labeling. 21 U.S.C. §§ 355(b)(1)(A) & 355(d); 21 C.F.R. §§ 314.50 & 314.125(b)(2), (3), (6). Because FDA's safety and effectiveness review is directly tied to the conditions of use according to the drug's labeling, FDA reviews the manufacturer's proposed labeling and must approve the precise language of the label's warnings and contraindications sections. 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.105(b) (approval of drugs is "conditioned" on use of labeling and warnings "exactly as directed" by FDA). FDA approval thus authorizes

the manufacturer to sell the drug so long as it bears the precise label reviewed and approved by FDA.

FDA generally must pre-approve any changes to the drug's label after approval; after all, FDA's rigorous review of the precise label language in connection with its approval decision would be meaningless if the manufacturer could make significant changes to the label on a unilateral basis after approval. 21 C.F.R. § 314.70(b); 21 C.F.R. § 314.81. A manufacturer must formally file a "supplement" to its New Drug Application to effect any change to the label (aside from minor editorial changes). Ordinarily, the supplement must be submitted to FDA as a "Prior Approval Supplement," meaning that FDA must review and approve the proposed change before it may be implemented. 21 C.F.R. § 314.70(b)(2)(v); *see also* 21 C.F.R. § 314.70(b)(3) ("The applicant must obtain approval of [the] supplement from FDA prior to distribution of a drug product made using [such] a change.").

B. FDA's CBE Regulation Permits A Manufacturer To Change Its Label Before Obtaining FDA Approval Only If Newly Acquired Information Reasonably Establishes A Causal Relationship Between The Drug And New Risks.

FDA's "Changes Being Effected" regulation creates a narrow exception to the usual "Prior Approval Supplement" procedure. In fact, certain CBE supplements must still be submitted to FDA "at least 30 days prior to the distribution of the drug product made using the change." 21 C.F.R. § 314.70(c). Such supplements—sometimes called "CBE-30" supplements—differ from Prior Approval Supplements in that the manufacturer may implement the proposed change 30 days after submitting the supplement unless FDA directs otherwise. 21 C.F.R. § 314.70(c). In certain limited circumstances, however, a manufacturer may unilaterally change certain sections of a drug's label at the same time it submits a CBE supplement. For this subset of CBE supplements—sometimes called "CBE-0" supplements—the manufacturer may "commence distribution of the drug product involved upon receipt by the agency of" the supplement. 21 C.F.R. § 314.70(c)(6).

The plain terms of the CBE regulation limit the circumstances under which a manufacturer may invoke it to avoid the usual Prior

Approval Supplement procedure. As an initial matter, a manufacturer may use the CBE process to make only certain kinds of changes to its label, such as to add or strengthen a contraindication, warning, or precaution. 21 C.F.R. § 314.70(c)(6)(iii)(A). But the CBE regulation does not authorize any addition or strengthening of a warning that the manufacturer may wish to make. Instead, it imposes two significant requirements, one temporal and one substantive.

First, the change must be based on "newly acquired information," 21 C.F.R. § 314.70(c)(6)(iii)(A), defined as data not previously submitted to FDA or new analyses of previously submitted data if the new analyses "reveal risks of a different type or greater severity or frequency than previously included in submissions to the FDA." 21 C.F.R. § 314.3(b). This limitation ensures that a manufacturer cannot simply second-guess FDA's label decision; it limits CBE changes to situations where FDA has not yet made an updated label decision because it has not yet considered new information that became available only after FDA approved the existing label language.[3]

[3] This definition places no limitation on *who* must submit the information to FDA for it to be regarded as previously submitted. Nor would it make sense to assume that only data submitted by

FDA made the "newly acquired information" requirement explicit in a 2008 amendment to the CBE regulation, but the regulation had contained that requirement since its initial promulgation in 1982. *New Drug and Antibiotic Regulations*, 47 Fed. Reg. 46,622, 46,623 (Oct. 19, 1982) ("[S]ome information, although still the subject of a supplement, would no longer require agency preclearance. These supplements would describe changes placed into effect to correct concerns about newly discovered risks from the use of the drug."); *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008) (explaining that "FDA proposed what is essentially the current CBE procedure in 1982. When proposed, the agency made clear that CBE supplements were intended to apply only if the sponsor became aware of newly discovered safety information that was appropriate for inclusion in the

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manufacturers counts. Instead, what matters is that FDA saw, assessed, and reached its own conclusions about scientific evidence related to a drug. Consider, for example, FDA's response to comments submitted regarding its 2008 labeling regulations. *See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49,603, 49,606-07 (Aug. 22, 2008). The very regulations that supply the legal standard at issue were crafted in response to *citizen* comments. FDA's response is no less entitled to deference, even though it responded to submissions from citizens and not only manufacturers.

labeling for the product."). The 2008 rulemaking made clear that it was "intended only to codify the agency's interpretation of current policy," and did not "substantively change the standards for submission of CBE or [Prior Approval] supplements." *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49,603, 49,608, 49,606 (Aug. 22, 2008); *see also id.* at 49,608 ("[T]he purpose of the final rule is to clarify that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information…. FDA does not consider this to be a substantive policy change, and it does not alter the agency's current practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement.").

Second, the CBE regulation authorizes an added or strengthened warning "*only if* there is sufficient evidence of a causal association" between the drug and risks of a different type or greater severity or frequency than already addressed in the label. *See id.* at 49,604 (emphasis added); *id.* at 49,608. FDA has explicitly stated that it defines "sufficient evidence of a causal association" for this purpose in the same way as that phrase is "defined in other FDA regulations and

guidance documents." *Id.* at 49,603.[4] Although "a causal relationship need not have been definitely established," there must be "*reasonable evidence* of a causal association with a drug." 21 C.F.R. § 201.57; *see also In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 951 F. Supp. 2d 695, 704 (D.N.J. 2013) (explaining that a proposed CBE change must be based on "reasonable evidence of an association between a hazard and the drug at issue"), *appeal pending*, No. 14-1900 (3d Cir.).

Overwarning can deter patients from taking needed medications, so FDA has consistently and explicitly required for over thirty years that warnings be based on "reasonable evidence … [of] an association between a drug and a serious hazard." 44 Fed. Reg. 37,434, 37,436 (June 26, 1979); 21 C.F.R. § 201.57; 21 C.F.R. § 201.80. And even

[4] "The phrase 'sufficient evidence of a causal association' refers to the standards for drugs and biologics described in § 201.57(c)(6) (21 CFR 201.57(c)(6)) (for Warnings and Precautions—'reasonable evidence'), and in § 201.57(c)(7) (21 CFR 201.57(c)(7)) (for Adverse Reactions—'some basis to believe') and to the standard for devices in the Device Labeling Guidance, General Program Memorandum G91-1 (March 8, 1991) (http://www.fda.gov/cdrh/g91-1.html) ('reasonable evidence') for the level of evidence needed to support a causal association with these medical products." *Supplemental Applications*, 73 Fed. Reg. at 49,604. (Section 201.57 was amended in 2006; the standard for "older drugs" like Clomid is now located at 21 C.F.R. § 201.80.)

though commenters had "argue[d] that public policy should not discourage sponsors from warning, *even when the regulations do not require it*," FDA stood by its "uniform standards for drug labeling," emphasizing—sensibly enough—that it "seek[s] to ensure that scientifically sound information is provided in the labeling of the drug." *Supplemental Applications*, 73 Fed. Reg. at 49,604 (emphasis added).

Finally, although the CBE regulation authorizes immediate implementation of a change that meets these criteria, FDA retains the ultimate authority to accept or reject the change—and the same legal standards apply to FDA's review of a CBE change as to its review of a Prior Approval Supplement. *In re Depakote*, 87 F. Supp. 3d 916, 923 (S.D. Ill. 2015) ("FDA applies the same standards to evaluate *both PAS and CBE* supplements" (emphasis added)).

C. Requiring A Manufacturer To Make A CBE Change Not Authorized Under The CBE Regulation Would Require It To Violate Federal Law.

The FDCA prohibits introducing misbranded drugs into interstate commerce, misbranding drugs, receiving or delivering misbranded drugs, manufacturing misbranded drugs, and "doing any other act" that results in misbranding. 21 U.S.C. §§ 331(a), (b), (c), (g), (k). If a

manufacturer sells a drug that is not accompanied by its FDA-approved labeling, that act in itself constitutes misbranding. *See, e.g.*, *In re Celexa*, 779 F.3d at 36 ("After approval, the manufacturer may distribute the drug without violating federal law as long as it uses the FDA-approved label."). FDA approval of a New Drug Application is expressly "conditioned" on the use of "final printed labeling" (prescribing information) that is identical to the proposed labeling that accompanies the approval letter. *See* 21 C.F.R. § 314.105(b) (approval is "conditioned" on use of labeling and warnings "exactly as directed" by FDA). In addition, a drug is "misbranded" if its "labeling is false or misleading." 21 U.S.C. § 352(a); *see* 39 Fed. Reg. 33,229, 33,232 (Sept. 16, 1974) ("The presence of unsubstantiated medical opinion in drug labeling would be misleading within the meaning of sections 502(a) and 201(n) of the act.").

As noted above, the CBE regulation provides a limited exception to the requirement that a manufacturer use only the label previously approved by FDA. Neither the FDCA nor any other FDA regulation creates any other exception to that requirement, so if the CBE regulation does not authorize a change from the FDA-approved label,

federal law does not authorize that change. If a manufacturer invokes the CBE regulation to make a label change that does not meet that regulation's standards, it violates federal law. Accordingly, where "newly acquired information" does not justify the label change allegedly required by state law, the manufacturer may not make that change via a CBE supplement. Similarly, if new information exists, but it does not "reveal risks of a different type or greater severity or frequency" than already addressed by the FDA-approved label, the CBE regulation does not authorize a change. And if a manufacturer makes a CBE change to add a warning not substantiated by "sufficient evidence of a causal association" with the hazard at issue, it likewise misbrands the drug. In any of these scenarios, selling the drug with a label reflecting an unauthorized change would violate the FDCA's bans on introducing and distributing misbranded drugs in interstate commerce. 73 Fed. Reg. 49,603; *see* 21 U.S.C. § 331(a), (b), (c), (k).

That is precisely why courts recognize that effecting a label change through, but not authorized by, the CBE regulation constitutes misbranding. "It is technically a violation of federal law to propose a CBE that is not based on reasonable evidence." *Mason v. SmithKline*

Beecham Corp., 596 F.3d 387, 392 (7th Cir. 2010); *see In re Incretin-Based Therapies Prod. Liab. Litig.*, 142 F. Supp. 3d at 1120 ("Unapproved labeling could be considered misbranded and subject to an FDA enforcement action."); *In re Depakote*, 87 F. Supp. 3d at 923 ("labeling remains subject to enforcement action" (citation omitted)). Under the FDCA, misbranding can carry serious consequences for manufacturers and individuals. *See* 21 U.S.C. §§ 332-334 (injunctive relief, fines, imprisonment, and seizure).

To the extent that plaintiffs' appeal rests on the premise that a brand-name drug manufacturer may always use the CBE process to make a label change allegedly required by state law, plaintiffs ignore the legal standards that apply under that regulation. And to the extent that plaintiffs' appeal rests on the premise that state law may require a manufacturer to make a CBE change *not* authorized by federal law, plaintiffs ignore the Supreme Court's holdings about the meaning of "impossibility" in the specific context of FDA approval of drug warning labels. Because Aventis could not have made the label change that plaintiffs say state law required unilaterally and consistently with federal law, plaintiffs' claims are preempted. That would be true as a

matter of law even if FDA had not considered and rejected the label change advocated by plaintiffs, but FDA's thorough consideration and explicit rejection of that change eliminates any doubt that preemption applies here.

CONCLUSION

For the reasons set forth in Aventis's brief and in this brief, the Court should affirm the district court's judgment holding plaintiffs' claims to be preempted by federal law.

Respectfully submitted,

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Dated: September 19, 2016.

CERTIFICATE OF SERVICE

I hereby certify that I filed the foregoing *Amici Curiae* Brief with the United States Court of Appeals for the Tenth Circuit with notice to be generated and sent electronically by the Court's ECF system to all designated persons this 19th day of September, 2016.

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This brief complies with the type-volume limitation of Fed. R. App. P. 29(d) and 32(a)(7)(B) because this brief contains 6,049 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point Century Schoolbook font. I relied on the word count of that software to obtain the word count above.

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Per the Court's CM/ECF User's Manual, the undersigned certifies as follows:

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