

United States Court of Appeals For the First Circuit

No. 25-1268

ELISSA E. WARNER, as Personal Representative of the Estate of
Decedent Lucas Joseph Warner,

Plaintiff, Appellant,

v.

AMGEN INC.; AMGEN USA INC.,

Defendants, Appellees,

NOVARTIS INSTITUTE FOR BIOMEDICAL RESEARCH, INC.,

Defendant.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

[Hon. Julia E. Kobick, U.S. District Judge]

Before

Montecalvo, Lipez, and Kayatta,
Circuit Judges.

Abbye R. K. Ognibene, with whom Thomas M. Sobol, Mark T. Vazquez, and Hagens Berman Sobol Shapiro LLP were on brief, for appellant.

Jessica L. Ellsworth, with whom Lauren S. Colton, Maria R. Durant, Johannah Cassel-Walker, and Hogan Lovells US LLP were on brief, for appellees.

October 9, 2026

KAYATTA, Circuit Judge. This appeal arises out of a wrongful death suit concerning the prescription medication Aimovig, a biologic manufactured by Amgen Inc. and Amgen U.S.A. Inc. (collectively, "Amgen") for the prevention of migraines. Lucas Warner, who had a history of seizures and cerebrovascular disease, died at the age of twenty-five from cerebrovascular complications after taking a single dose of Aimovig. His mother, Elissa Warner,¹ challenged under state law the adequacy of the drug's label as originally approved by the U.S. Food and Drug Administration (FDA, or the "agency"). The district court dismissed Warner's complaint, finding her claims preempted by the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 et seq. The court also denied Warner leave to amend her complaint to include allegations that Amgen should have supplemented its label after it was initially approved but before Lucas received the drug, finding that such an amendment would be futile.

We affirm the district court's dismissal of Warner's original complaint but reverse the court's decision to deny Warner leave to amend her complaint. Our reasoning follows.

¹ For consistency with the proceedings below, we refer to Lucas Warner as "Lucas" and his mother as "Warner."

I.

A.

We begin with the regulatory framework underpinning this appeal. In 1962, Congress amended the FDCA, "shift[ing] the burden of proof" for drug safety and labeling "from the FDA to the manufacturer." Wyeth v. Levine, 555 U.S. 555, 567 (2009). Under the amended FDCA, a manufacturer seeking FDA approval of a license to market a drug must "demonstrate that its drug [is] safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling before it [can] distribute the drug." Id. (citation modified); 21 U.S.C. § 355(b)(1). Prior to marketing a pharmaceutical drug, a manufacturer must submit a new drug application (NDA) that meets the requirements for FDA approval promulgated under 21 C.F.R. § 314.50(c). See Wyeth, 555 U.S. at 566; 21 C.F.R. § 314.50.

Aimovig is a biologic product. Biologic products -- which include viruses, vaccines, blood components, allergenic products, and proteins -- are a "type of drug," though they are "derived from natural, biological sources" rather than "synthesized from chemicals" like typical drugs. Sandoz Inc. v. Amgen Inc., 582 U.S. 1, 6 (2017); see also 42 U.S.C. § 262(i)(1) (defining "biological product").² Like other drugs, biologic

² The parties use the term "biologic product," whereas the statute and regulations refer to "biological product[s]." See 42

products are regulated under the FDCA. 42 U.S.C. § 262(j). The licensing of biologic products is nevertheless governed primarily by section 351 of the Public Health Service Act (PHSA), 42 U.S.C. § 262.³ Thus, rather than submit an NDA to obtain permission to market a new drug, a biologic manufacturer must instead submit to the FDA a Biologics License Application (BLA) under the PHSA. 21 C.F.R. § 601.2(a).

Notwithstanding the differing regulatory authorities for licensing biologics versus other drugs, for our purposes the approval process and the implications of that process are materially the same. Compare id., with 21 C.F.R. § 314.50. Manufacturers submitting a BLA are required, among other things, to "submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." 21 C.F.R. § 601.2(a). And they cannot market the drug until the FDA approves both the drug and its label. 42 U.S.C. § 262(a); see

U.S.C. § 262(i)(1); 21 C.F.R. § 601.2(a). For purposes of this appeal, we use the terminology of the parties and refer to Aimovig as a "biologic" or "biologic product."

³ See Frequently Asked Questions About Therapeutic Biological Products, FDA (May 16, 2024), <https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products> [<https://perma.cc/64F7-6BSQ>] (noting that "[b]iological products are a subset of drugs" that are "regulated under provisions of the [FDCA]," but "only biological products are licensed under section 351 of the [PHSA]").

also In re Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 35-36 (1st Cir. 2015) (explaining that "[t]he FDA will not approve a drug," and thus the drug cannot be marketed, "if the NDA or [supplemental NDA] lacks substantial evidence that the drug will have the effect it purports or is represented to have," but "[a]fter approval, the manufacturer may distribute the drug without violating federal law as long as it uses the FDA-approved label" (citation omitted)).

The FDA's process for reviewing a BLA submission and determining the appropriate content of a biologic's label involves (1) an FDA review committee that "[p]articipates in the labeling review to ensure the content and formatting of the label comply with requirements per applicable regulations"; (2) a regulatory project manager who oversees and coordinates the labeling review; (3) a clinical reviewer who "[e]nsures [the] accuracy of clinically relevant product information in the labeling"; (4) a clinical pharmacology reviewer who "[e]nsures [the] accuracy of mechanism of action statements, pharmacodynamics, pharmacokinetics, and information on the impact of age, sex, and race in the labeling"; (5) a chemistry manufacturing and control reviewer who "[e]nsures [the] accuracy of chemistry and manufacturing product information provided in the labeling"; (6) an advertising and promotional labeling branch reviewer who "[e]nsures the information in the labeling is not false or

misleading to the target audience(s)"; (7) a statistician; and (8) a non-clinical toxicologist reviewer. FDA Ctr. for Biologics Evaluation & Rsch., SOPP 8412: Review of Product Labeling 5-6 (2026), <https://www.fda.gov/media/81790/download> [<https://perma.cc/TY7V-H59X>]. The review committee is further tasked with "[c]omplet[ing] a thorough review of the labeling," meeting with the BLA applicant (in this case, the manufacturer), "identify[ing] labeling revisions," and "[s]end[ing] . . . revision requests" to the manufacturer. Id. at 8-9. When the manufacturer revises the draft labeling, the review committee and the regulatory project manager work together to confirm that the changes are consistent with the agency's requested revisions. Id. at 9.

Pursuant to FDA regulations, the contents of a drug label must include, in order (and among other things):

- (1) prominent "boxed" warnings about risks that may lead to death or serious injury;
- (2) contraindications describing any situation in which the drug should not be used because the risk of use outweighs any therapeutic benefit;
- (3) warnings and precautions about other potential safety hazards; and
- (4) any adverse reactions for which there is some basis to believe a causal relationship exists between the drug and the occurrence of the adverse event.

Merck Sharp & Dohme Corp. v. Albrecht, 587 U.S. 299, 304 (2019) (quoting 21 C.F.R. § 201.57(c)). The order in which these categories must appear is far from random; rather, "the category

in which a particular risk appears on a drug label is an indicator of the likelihood and severity of the risk." Id. With this "hierarchy of label information," the FDA assures that "more important information" is not "overshadowed" by "less important information." Id. (citation modified).

In approving the final label for a new drug or biologic, the FDA aims to warn of risks while at the same time "prevent[ing] overwarning, which may deter appropriate use of medical products." In re Zofran (Ondansetron) Prods. Liab. Litig., 57 F.4th 327, 330 (1st Cir. 2023) (quoting Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49605-06). The agency's final determinations are thus meant to "guard[] against the exaggeration of risk, or inclusion of speculative or hypothetical risks," id. (citation modified), such as "theoretical hazards not well-grounded in scientific evidence [that] can cause meaningful risk information to lose its significance," Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3935 (Jan. 24, 2006) (citation modified).

Only after this "onerous and lengthy" process is complete, Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 476 (2013), does the agency confirm its acceptance of a BLA or NDA with the manufacturer. Accordingly, the approval of a BLA "constitute[s]

a determination that the . . . product meet[s] applicable requirements to ensure the continued safety, purity, and potency" of biologics such that the product may enter the market. 21 C.F.R. § 601.2(d); see also 42 U.S.C. § 262(a)(2)(C).

After the FDA has approved a label, the manufacturer must usually obtain permission from the FDA before making any changes to it. See In re MDL 2700 Genentech Herceptin (Trastuzumab) Mktg. & Sales Prac. Litig., 960 F.3d 1210, 1236 (10th Cir. 2020); 21 C.F.R. § 601.12(f)(1)-(3) (describing the pathways available to manufacturers seeking to amend a biologic label). The so-called Changes Being Effected (CBE) regulations provide an exception, applicable to both general pharmaceutical drugs under 21 C.F.R. § 314.70(c)(6) and biologics under 21 C.F.R. § 601.12(f)(2).⁴ Under the CBE procedure, a manufacturer may without prior permission alter a drug or biologic's approved label based on "newly acquired information" in order to "accomplish" one of five possible labeling objectives provided by the regulations. 21 C.F.R. § 601.12(f)(2)(i)(A)-(E). Upon making such a labeling change, the manufacturer must submit a supplemental label to the FDA and may immediately begin using the revised label even as the

⁴ Though the regulations are largely analogous, the district court based its analysis on the CBE regulations pertaining to general pharmaceutical drugs under 21 C.F.R. § 314.70(c)(6) rather than those pertaining to biologic products under 21 C.F.R. § 601.12(f)(2).

FDA considers whether to approve the change. 21 C.F.R. § 601.12(f)(2)(ii).

B.

With this regulatory framework in mind, we turn to the facts of this case. Because this case was resolved on a motion to dismiss, we take as given the well-pleaded facts in the complaint. O'Brien v. United States, 155 F.4th 50, 53-54 (1st Cir. 2025).

Aimovig is the proprietary name for the biologic drug erenumab. "Erenumab is a human monoclonal antibody that antagonizes the calcitonin gene-related peptide (CGRP) receptor." Because CGRP plays "a role" in the development of migraines, Aimovig aims to prevent migraines by inhibiting CGRP's ability to bind to CGRP receptors. At the time of its BLA submission, Aimovig was "the first product of this class to be reviewed in an FDA marketing application."

Amgen submitted a biologics license application for Aimovig on May 17, 2017. Aimovig received FDA approval exactly one year later. The label as approved by the agency contained 12 sections, numbered (with some omissions) from 1 to 17.⁵ Section 14 of Aimovig's label, titled "Clinical Studies," states that

⁵ A biologic's label can contain up to 17 possible sections. See 21 C.F.R. § 201.57(c)(2)-(18) (listing all 17 possible sections). Sections number 5, 7, 9, 10, and 15 were omitted from Aimovig's label.

patients "with myocardial infarction, stroke, transient ischemic attacks, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening" were excluded from the drug's clinical trials. (Emphasis added). Warner criticizes that description because it failed to disclose that the Aimovig studies also excluded anyone who had ever suffered from seizures or neurological disorders. The label similarly noted no particular risk of Aimovig use for those in either of these clinical trial exclusion groups.

Knowing of these undisclosed exclusions would have been relevant to Lucas and his doctor, Warner alleges, because Lucas had suffered from "both seizures and cerebrovascular disease/surgery" more than a year prior to taking Aimovig. Lucas was diagnosed with an arteriovenous malformation⁶ (AVM) at the age of six that led him to have "frequent and severe migraines" as well as "periodic brain bleeds." In 2011 and then again in 2012, Lucas underwent an embolization⁷ to help treat his AVM and migraine

⁶ An arteriovenous malformation is an "improper or abnormal development related to arteries or veins." Arteriovenous Malformations (AVM), Stedman's Medical Dictionary 1147 (28th ed. 2006). With an AVM, "blood is shunted from arterioles to venules without passing through the capillaries." Id.

⁷ An embolization is the "[t]herapeutic introduction of various substances into the circulation to occlude vessels, either to arrest or prevent hemorrhaging, to devitalize a structure, tumor, or organ by occluding its blood supply, or to reduce blood flow to an arteriovenous malformation." Embolization, Stedman's Medical Dictionary, supra, at 627.

symptoms, though these procedures provided limited relief. In 2014, he suffered a subacute hemorrhage from his AVM.

In June 2018, unaware that persons with any history of seizures and neurological disease had been excluded from the Aimovig clinical trials, Lucas's doctor prescribed him Aimovig to treat his migraines. Lucas took one dose of Aimovig on June 17, 2018, at age twenty-three. Less than 48 hours later, Lucas suffered seizures and was placed in a coma. He experienced "multi-organ failure." His doctors believed that Aimovig had "cross[ed] [his] blood brain barrier,"⁸ thereby causing the seizures, and they "attempt[ed] to remove [Aimovig] from his brain and blood." Due to those seizures, Lucas "suffered significant irreversible brain damage, including the near-total loss of his short-term memory" and the inability to eat or drink. He struggled to walk and stand. He was left "cognitively severely impaired," forcing him to discontinue his university studies, as the doctors could not do anything "to reverse the damage caused by [Aimovig]." In 2020, Lucas's condition worsened, and he suffered repetitive seizures

⁸ The blood-brain barrier is "a selective mechanism" that "oppos[es] the passage of most ions and high molecular weight compounds from the blood to brain tissue." Blood-Brain Barrier, Stedman's Medical Dictionary, supra, at 205; see also In re Vertex Pharms. Inc., Sec. Litig., 357 F. Supp. 2d 343, 345 (D. Mass. 2005) ("The blood-brain barrier is a selective filter that regulates the transport of certain molecules from the blood to the brain, and protects the brain from substances in the blood that would cause undesirable effects in the brain.").

"due to temporal mesial sclerosis, a result of the brain damage" from Aimovig.

Lucas died on November 17, 2020. His death certificate lists his primary cause of death as "hypoxia respiratory failure" caused by "stroke," "refractory seizures," and "cerebral angiopathy."⁹ His death certificate also states that "complications from Aimovig" "contribut[ed]" to his death.

Warner filed a wrongful death complaint against Amgen in Massachusetts state court, alleging that her son died from medical complications due to taking Aimovig and asserting liability on a failure-to-warn theory. Warner alleged that Aimovig's label as approved by the FDA should have contained a warning that the biologic drug had not been tested on persons like Lucas with any history at all of "seizures or cerebrovascular disease/surgery," as well as a warning regarding the "complications suffered by Lucas."

Amgen removed the suit to the U.S. District Court for the District of Massachusetts. Amgen then filed a motion to dismiss for failure to state a claim pursuant to Federal Rule of

⁹ Hypoxia involves the "[d]ecrease below normal levels of oxygen in inspired gases, arterial blood, or tissue." Hypoxia, Stedman's Medical Dictionary, supra, at 939. "Refractory" seizures are seizures that are "resistant to treatment." Refractory, Stedman's Medical Dictionary, supra, at 1664. And angiopathy is "[a]ny disease of the blood vessels or lymphatics." Angiopathy, Stedman's Medical Dictionary, supra, at 88.

Civil Procedure 12(b)(6), contending (among other things) that because it was required to use the label approved by the FDA, and because Warner had not shown Amgen could have changed that label, federal law preempted Warner's state law claim that Aimovig's label should have disclosed more about the drug's clinical trial exclusions or the possible complications related to those exclusions.

At the motion hearing for Amgen's motion to dismiss, Warner introduced a new contention. In addition to critiquing Amgen's efforts to secure FDA approval of the label in the first instance, she contended that a series of studies and literature reviews not known to the FDA during the approval process would have allowed Amgen to employ the CBE procedure to change the label after it was approved and before Lucas took the drug. Such a change, argued Warner, would have mentioned not just the lifetime exclusion group, but also additional risks for patients like Lucas. Following argument, the court requested that Warner file a supplemental brief "including more information on studies identified" during the hearing.

With her supplemental brief, Warner submitted nine articles -- including studies and literature reviews, most of which were published before the FDA approved the label -- that she asserted qualified as newly acquired information that would have allowed Amgen to amend its approved label under the CBE procedure.

Warner argued that these articles "establishe[d] a reasonable basis for believing that a CGRP blockade pose[s] a type, severity, or frequency of risk that was not submitted to or analyzed by the FDA prior to Aimovig's approval." Warner also requested leave to amend her complaint to counter Amgen's affirmative preemption defense and to assert that, based on the studies and reviews presented, Amgen could have updated its label using the CBE process to reflect "cerebral risks presented by CGRP-blocking drugs, like Aimovig, that were not previously submitted to the FDA."

After reviewing Warner's submissions, the court concluded that "the articles [did] not plausibly constitute newly acquired information" and failed to "link Aimovig or any other CGRP-blocking drug to an adverse event or risk" that would have allowed Amgen to amend Aimovig's label. Warner v. Amgen Inc., No. 24-CV-10632, 2025 WL 490720, at *9 (D. Mass. Feb. 13, 2025). The court further surmised that because the FDA had "reviewed 'the world's literature'" on "the theoretical risks associated with CGRP antagonism," it was "not plausible that articles bearing on that subject" that were published before the FDA began its review would constitute newly acquired information not previously considered by the FDA. Id. at *10. As to Warner's argument that, pre-approval, Amgen should have submitted a proposed label to the FDA disclosing that patients like Lucas had been excluded from Aimovig's trials, the court found that "the FDA was aware that

individuals who had ever been diagnosed with a seizure disorder or cerebrovascular disease were excluded from Aimovig's clinical trials" and that the FDA "considered the risks and safety concerns associated with these exclusions" before approving a label lacking any disclosure of them. Id. at *8. Accordingly, the court granted Amgen's motion to dismiss with prejudice and denied Warner's request for leave to amend her complaint as futile. Id. at *12. This appeal followed.

II.

This court "review[s] the grant of a motion to dismiss de novo, accepting well-pled facts as true and drawing all inferences in favor of the non-moving party." O'Brien, 155 F.4th at 53-54 (quoting 3137, LLC v. Town of Harwich, 126 F.4th 1, 8 (1st Cir. 2025)). To survive dismissal for failure to state a claim under Rule 12(b)(6), a complaint must "'state a claim to relief that is plausible on its face,'" such that we can "draw the reasonable inference that the defendant is liable for the misconduct alleged." Ashcroft v. Iqbal, 556 U.S. 662, 678 (2009) (quoting Bell Atl. Corp. v. Twombly, 550 U.S. 544, 570 (2007)). We are mindful that this plausibility requirement does not "impose a . . . requirement" of probability. Twombly, 550 U.S. at 556. On the other hand, a "sheer possibility" is not enough. Iqbal, 556 U.S. at 678. As such, "[t]he relevant inquiry focuses on the reasonableness of the inference of liability that the plaintiff is

asking the court to draw from the facts alleged in the complaint." Ocasio-Hernández v. Fortuño-Burset, 640 F.3d 1, 13 (1st Cir. 2011).

On appeal, Amgen does not contend that Warner's complaint fails to state a plausible claim for relief under applicable state law. Rather, Amgen argues that the district court correctly found that Amgen's affirmative defense -- federal preemption -- defeats Warner's state-law claim before it gets out of the starting blocks. See PLIVA, Inc. v. Mensing, 564 U.S. 604, 619 (2011) (referring to preemption as an affirmative defense); Durnford v. MusclePharm Corp., 907 F.3d 595, 603 n.8 (9th Cir. 2018) ("FDCA preemption, like all federal preemption, is an affirmative defense.").

When an order of dismissal under Rule 12(b)(6) is "premised on the inevitable success of an affirmative defense," we will uphold the order so long as (1) "the facts establishing the defense are definitively ascertainable from the complaint and the other allowable sources of information" and (2) "those facts suffice to establish the affirmative defense with certitude." Burt v. Bd. of Trs. of Univ. of R.I., 84 F.4th 42, 50 (1st Cir. 2023) (quoting Nisselson v. Lernout, 469 F.3d 143, 150 (1st Cir. 2006)); see also Scheibe v. ProSupps USA, LLC, 141 F.4th 1094, 1098 (9th Cir. 2025) ("Under Rule 12(b)(6), only when the plaintiff pleads itself out of court, by admitting all the elements of an

affirmative defense, may a complaint that otherwise states a claim be dismissed." (citation modified)).

III.

This appeal does not call on us to apply a statutory preemption clause. Cf. Monsanto Co. v. Durnell, 146 S. Ct. 2001, 2006 (2026) (reviewing an express preemption clause contained in 7 U.S.C. § 136v(b)). Rather, Amgen's FDCA preemption defense rests on the proposition that it was not legally possible to use a label other than the label originally approved by the FDA. This type of preemption is often called impossibility preemption, which exists "where it is impossible for a private party to comply with both state and federal requirements." Zofran, 57 F.4th at 335-36 (citation modified).

Impossibility preemption "is a demanding defense." Wyeth, 555 U.S. at 573. As a general matter, there is a presumption against preemption. See id. at 565 ("[W]e start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." (citation modified)). In the prescription drug context, the drug manufacturer bears the ultimate burden of establishing a preemption defense. See Albrecht, 587 U.S. at 313-14.

Warner claims in support of her complaint that it would have been possible for Amgen to comply with Massachusetts state

law by proposing a better label when originally seeking FDA approval. Alternatively, she claims in support of her motion to amend her complaint that Amgen could have later changed the approved label. We assess each claim in turn.

A.

We begin with what the parties call Warner's "pre-approval" theory, which is the theory tendered in support of her complaint. In substance, Warner asserts that, in its BLA submission to the FDA, Amgen could have proposed a label disclosing that Aimovig's clinical trials excluded "people with a history of seizures" or "cerebrovascular disease/surgery" at any time in their lives. Such a disclosure would have revealed that "potential complications related to those exclusions" could have escaped notice in the clinical trials.

We see two flaws in this argument, one legal and one factual, each sufficient to sustain the dismissal of Warner's complaint. First, as a matter of law, a manufacturer's ability to ask the FDA to include something in a label falls short of the unilateral power required to preclude an impossibility preemption defense. Second, as a matter of fact, the record in this case is clear that the FDA would have rejected a request to further describe in the label the exclusions from Aimovig's clinical trials. We explain these independent grounds for affirming dismissal in turn below.

1.

"[W]hether a private party can act sufficiently independently under federal law to do what state law requires may sometimes be difficult to determine." PLIVA, 564 U.S. at 623. Indeed, the Supreme Court itself has recognized that prescription drug preemption matters "h[ave] repeatedly vexed the Court -- and produced widely divergent views -- in recent years." Bartlett, 570 U.S. at 492-93 (citing Wyeth, 555 U.S. 555, and PLIVA, 564 U.S. 604). That puzzlement arises in part due to the lack of congressional clarity regarding preemption in federal law: "[T]he FDCA's treatment of prescription drugs includes neither an express pre-emption clause (as in the vaccine context, 42 U.S.C. § 300aa-22(b)(1)), nor an express non-preemption clause (as in the over-the-counter drug context, 21 U.S.C. §§ 379r(e), 379s(d))." Id. at 493. This lack of clarity leaves courts to "divine Congress' will from the duties the statute imposes." Id. So we do our best, following the guidance provided by the Supreme Court and our own circuit precedent.

We start with Wyeth. If Warner were correct that a manufacturer's ability to ask the FDA to include certain language on a label precluded an impossibility preemption defense to a claim that the label was insufficient, then the Supreme Court in Wyeth would have had little reason to hinge its discussion on the availability of the CBE procedure. The Court could have simply

rested its decision on whether it was possible for the manufacturer to request that the FDA take certain action -- in this case, to approve a change to the label. Indeed, the Court's segue from noting the manufacturer's ability to request approval to focusing instead on the CBE procedure strongly suggests that the Court presumed that the mere ability to request approval of a change did not defeat the preemption defense. See Wyeth, 555 U.S. at 568 ("There is, however . . . the 'changes being effected' (CBE) regulation." (emphasis added)).

This suggestion grew stronger yet with the Court's discussion of Wyeth in PLIVA. There, the Court held that a generic drug manufacturer's ability to ask the FDA to change a drug's label did not defeat an impossibility defense. PLIVA, 564 U.S. at 619-21. In so holding, the Court explained that "[t]he question for 'impossibility' is whether the [defendant] could independently do under federal law what state law requires of it." Id. at 620. In that context, where state law required a stronger label, "[t]he only action the [m]anufacturers could independently take -- asking for the FDA's help -- [was] not a matter of state-law concern." Id. at 624. Because requesting that the FDA take action was simply the first step in a chain of contingencies that, with the FDA's help, "might have eventually" -- but could not have independently -- yielded the requisite stronger warning label, the Court found such a claim to be preempted. Id. at 620-21; see also

id. at 623-24 ("To decide these cases, it is enough to hold that when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes.").

As we subsequently stated in Celexa, the PLIVA 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." 779 F.3d at 41 (citation modified); see also PLIVA, 564 U.S. at 624 (reasoning that Wyeth was not contrary to its holding because a brand-name manufacturer like the one in Wyeth can use the CBE process "to unilaterally strengthen its [drug's] warning" or label without prior FDA approval, whereas a generic manufacturer cannot (quoting Wyeth, 555 U.S. at 573)). And then more recently in Albrecht, the Supreme Court again turned its attention not to a manufacturer's ability to plead with the FDA for a labeling change, but rather to the CBE regulation allowing a change by the manufacturer "without prior approval from the FDA." 587 U.S. at 315. We have gathered from these cases a general principle: Where "a private party . . . cannot comply with state law without first obtaining the approval of a federal regulatory agency, then the application of that law to that private

party is preempted." Gustavsen v. Alcon Lab'ys, Inc., 903 F.3d 1, 9 (1st Cir. 2018).

And while the foregoing cases all apply this principle in the context of considering claims that approved labels should have been revised post-approval, we see no reason not to apply it to claims that the manufacturer should have submitted a different label in its BLA submission to the FDA. It follows, then, that a pre-approval claim like Warner's cannot survive a manufacturer's impossibility defense because a BLA submission is, by its nature, a request for agency approval.¹⁰

¹⁰ This is not to say that a manufacturer remains free to mislead the FDA in the approval process. While impossibility preemption bars a pre-approval claim based on a manufacturer's failure to propose a different label to the FDA, the enforcement mechanisms crafted by Congress to protect consumers against misleading or fraudulent actions by manufacturers remain in place. The FDCA prohibits manufacturers from obscuring information from or presenting false information to the FDA in their drug applications. See 21 U.S.C. § 331(a) (prohibiting introduction into interstate commerce of any drug "that is . . . misbranded"); id. § 352(a)(1) (deeming a drug misbranded where "its labeling is false or misleading in any particular"); see also Yousefzadeh v. Johnson & Johnson Consumer Inc., 184 F.4th 130, 141 (2d Cir. 2026) ("The misbranding provision . . . prohibits not only affirmative misrepresentations but also failures to disclose material facts."); United States v. Watkins, 278 F.3d 961, 964 (9th Cir. 2002) (describing misdemeanor and felony misbranding provisions under the FDCA).

And, as we will explain, information not submitted to the FDA in the approval process may serve as newly acquired information, requiring a post approval change in the label by the manufacturer to avoid liability under state law.

2.

Adding belt to suspenders, the record in this case makes clear that any pre-approval request by Amgen for the label Warner says it should have proposed would have been denied -- and indeed, was effectively denied. Certainly, the FDA was aware that the clinical trials submitted in support of Aimovig's application excluded persons with any history of "seizure disorders" or "significant neurological conditions." We know that because the summary of the studies prepared by the FDA's Division of Neurology Products (DNP) expressly mentioned those exclusions. The DNP further remarked in its clinical review and integrated safety assessment that "the selection criteria for the migraine studies resulted in a relatively young, healthy population" that excluded individuals suffering from "seizure disorders" or "major neurological disorders."

Indeed, Aimovig's DNP reviewer initially proposed adding a warning of "theoretical concern" for all "patients with major . . . cerebrovascular disease" (e.g., persons like Lucas). That recommendation was rejected after further internal review, as the FDA's Division of Risk Management determined that, despite the "theoretical" cerebrovascular risks posed by CGRP antagonism, there was "insufficient evidence to include th[e] theoretical risk in labeling." The FDA also rejected the DNP's suggestion to add a caution against Aimovig use in "[p]atients who ha[d] experienced

a stroke, myocardial infarction, transient ischemic attack, unstable angina or had coronary artery bypass surgery within the last year."

Ultimately, the final label as approved by the FDA contained no contraindications, warnings, or precautions, and it listed only "injection site reactions and constipation" as the "most common adverse reactions" to taking Aimovig. And while the "Clinical Studies" section disclosed that patients who had suffered from certain medical conditions, such as "myocardial infarction, stroke, [and] transient ischemic attacks . . . within 12 months prior to screening" had been excluded from Aimovig's clinical trials, the label did not disclose the lifetime exclusion criterion and included no warning, direct or otherwise, of the theoretical risk left unresolved by the design of the clinical studies.¹¹

Bearing in mind the FDA's knowledge of the clinical trial exclusion criteria and its clear consideration and rejection of added language to account for those exclusions, we are not free to

¹¹ Warner would have us discount the FDA's consideration of these excluded populations and the risk thereto because, in Warner's view, the FDA trained its attention more (but not exclusively) on cardiovascular risks than on cerebrovascular risks, as "evidenced" by Warner's counting of the number of references to cardiovascular versus cerebrovascular risks in the FDA's review. But there was good reason for the FDA to home in on cardiovascular considerations: "There were two deaths in the [Aimovig] database" of the clinical trials, and "both were cardiovascular-related sudden deaths."

disregard the FDA's final approval of an Aimovig label detailing only the description of the twelve-month exclusion (but not the lifetime exclusion) and conveying that exclusion as and where it did. It is true that no one proposed the FDA should word the label precisely as Warner says it should have been worded. But as we have described, the only reason to make such a change would be to flag the theoretical risks the agency had already decided did not warrant mentioning. We must therefore read the FDA's inclusion of the twelve-month exclusion in the Clinical Studies section of the label -- but not the lifetime exclusion -- as "constitut[ing] [the agency's] determination," 21 C.F.R. § 601.2(d), that the description of the clinical studies on the approved label would "facilitate an understanding of how to use the drug safely and effectively," id. § 201.57(c)(15). In the same manner, we must read the agency's omission of any indication, contraindication, warning or precaution, or adverse reaction related to the clinical trial exclusion criteria as the FDA's determination that the label as approved would be adequate to ensure the "safety, purity, and potency" of Aimovig such that it could enter the market. Id. § 601.2(d). As such, the agency's formal approval of the Aimovig label made clear that the agency would have rejected a suggestion by Amgen to include in the approved label the language that Warner says state law required. "[W]hen the FDA formally approves a label stating one thing with

full and obvious notice of the directly contrary position, one can read the approval as rejecting the contrary position." Zofran, 57 F.4th at 343.

* * *

In sum, we conclude that the district court correctly found that Warner's complaint did not survive Amgen's preemption defense. Amgen's ability to have proposed a different original label does not defeat its preemption defense because it did not have the ability to act unilaterally in the context of this "pre-approval" claim. And, in any event, it is clear that the FDA would have rejected the type of label Warner proposes in her complaint even if Amgen had requested it.

B.

We turn next to the district court's denial of Warner's request for leave to amend her complaint. In her request, Warner sought to add a claim based on a new theory of recovery that, post-approval, Amgen should have amended its label of its own accord using the CBE procedure to reflect newly acquired information. The district court determined that Amgen could not have revised its FDA-approved label as Warner alleged it should have; hence, the request to file an amended complaint was futile. Warner, 2025 WL 490720, at *12.

"A district court's ruling under Rule 15(a) that amendment would be futile 'means that the complaint, as amended,

would fail to state a claim upon which relief could be granted.'" D'Agostino v. ev3, Inc., 845 F.3d 1, 6 (1st Cir. 2016) (quoting Glassman v. Computervision Corp., 90 F.3d 617, 623 (1st Cir. 1996)); see also Fed. R. Civ. P. 15(a). We therefore review the district court's ruling de novo. D'Agostino, 845 F.3d at 6. In so doing, we ask whether the proposed amended complaint would have stated a plausible claim for relief that would not have been certainly precluded by Amgen's preemption defense. See Burt, 84 F.4th at 50.

Warner's proposed amendment to the complaint would have added reference to nine studies or articles advancing her new argument that, in light of any or all of the articles' findings, Amgen could have unilaterally changed Aimovig's approved label to add a warning that blocking CGRP disrupts neuroprotective mechanisms in the setting of cerebral injury. This argument puts in play consideration of the CBE procedure set forth at 21 C.F.R. § 601.12(f)(2). That procedure allows a manufacturer to change an approved label -- and then distribute the drug with the changed label before receiving FDA approval of the changes -- when, as relevant here, the added information "reflect[s] newly acquired information" that "add[s] or strengthen[s] a contraindication, warning, precaution, or adverse reaction." 21 C.F.R. § 601.12(f)(2)(i)(A).

The Supreme Court has considered several times how the availability of the CBE procedure bears on the adjudication of a preemption defense when a person challenges the adequacy of the warnings on a label previously approved by the FDA. See Wyeth, 555 U.S. 555; Albrecht, 587 U.S. 299. So, too, has this court. See, e.g., Celexa, 779 F.3d 34; Zofran, 57 F.4th 327.

Keeping in mind that we are reviewing the viability of an affirmative defense to reject a proposed pleading without the benefit of discovery, expert testimony, or fact finding, we must be left with "certitude" that Warner does not have a plausible basis for undercutting Amgen's affirmative defense in order to affirm the district court's denial of Warner's motion for leave to amend. Burt, 84 F.4th at 50 (citation modified); see also In re Colonial Mortg. Bankers Corp., 324 F.3d 12, 16 (1st Cir. 2003) (holding that, to dismiss a case based on an affirmative defense, "the facts that establish the defense must be definitively ascertainable from the allegations of the complaint" and other allowable sources, and "the facts so gleaned must conclusively establish the affirmative defense"). So, what need Warner plausibly show in order to rely on the CBE procedure at this stage of the lawsuit?

First, the parties appear to agree that Warner must plausibly allege facts establishing a "reasonable basis" for treating the articles she identifies as constituting "newly

acquired information." See Zofran, 57 F.4th at 336 (emphasis omitted) (reasoning that "Albrecht can arguably be read as . . . deeming the CBE procedure unavailable if there is no reasonable basis for treating the information identified by plaintiffs as newly acquired information" (citing Albrecht, 587 U.S. at 315)). The requirement that the information be "newly acquired" preserves the FDA's role as "the exclusive judge of safety and efficacy based on information available at the commencement of marketing, while allowing the states to reach contrary conclusions when new information not considered by the FDA develops."¹² Celexa, 779 F.3d at 41.

Second, Warner must plausibly allege facts showing that the proposed change is "for the purpose of accomplishing" -- as relevant here -- the objective of "add[ing] or strengthen[ing] a contraindication, warning, precaution, or adverse reaction." Id. at 37; see also 21 C.F.R. § 601.12(f)(2)(i)(A) (parallel regulation for biologics).

Third, because Warner argues that Amgen should have invoked the CBE procedure to add a warning, precaution, or adverse effect to Aimovig's label, she must also plausibly allege facts showing Amgen could have satisfied the causal association standard

¹² By "available" information we refer to information that would not be "newly acquired" if submitted after approval. See 21 C.F.R. §§ 314.70(c)(6)(iii), 601.12(f)(6).

set forth in 21 C.F.R. § 201.57(c) for those additions to the label. 21 C.F.R. § 601.12(f)(2)(i)(A). That standard requires either "reasonable evidence of a causal association" between "a clinically significant hazard" and a drug, id. § 201.57(c)(6)(i) (emphasis added), or "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event," id. § 201.57(c)(7) (emphasis added).

If Warner successfully makes the three foregoing showings, then Amgen's preemption defense fails unless Amgen can "show that the FDA, after being fully informed of the case for making [Warner's] proposed label change, made clear through agency action having the force of law that it would not have allowed the change had the defendant initiated it through the CBE procedure." Zofran, 57 F.4th at 342. With that framework in mind, we next consider the parties' submissions.

1.

We begin with the threshold issue of determining whether the articles submitted by Warner present a "reasonable basis for treating the information . . . as newly acquired information." Id. at 336 (emphasis omitted).

Newly acquired information is defined as "data, analyses, or other information not previously submitted to the [FDA]," which may include "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted

data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." 21 C.F.R. §§ 601.12(f)(6), 314.3(b). In Zofran, the parties all assumed that "determining whether certain information is 'newly acquired' [constituted] a legal question." 57 F.4th at 337. So we similarly assumed. Id. Here, too, the parties also treat the question as one of law, so we shall, too. That assumption still leaves room for fact finding. For example, the adjudicator may need to decide how significant the information is, whether it may qualify as new, and so on. Albrecht, 587 U.S. at 317. But resolution of these "brute facts . . . relevant to a court's legal determination" is "subsumed" under the court's legal analysis. Id.

In support of her motion for leave to amend her complaint, Warner posits that the nine articles she submitted "show increasing knowledge about cerebrovascular risk that would have enabled Amgen to supplement its label." Warner argues that the district court's conclusion that these studies did not qualify as newly acquired information was in error because "[t]he FDA -- at most -- knew about the vasodilatory¹³ effects of CGRP" but

¹³ Vasodilatory refers to dilation of the blood vessels. See Vasodilator, Stedman's Medical Dictionary, supra, at 2092.

"conduct[ed] no analysis of the specific risks of CGRP-inhibition in the brain and the non-vasodilatory roles of CGRP."

Turning to the nine articles submitted by Warner, we first set aside the 2018 Zhao¹⁴ and the 2018 Szeto¹⁵ literature reviews. The Zhao literature review suggests that remote ischemic postconditioning may offer cerebral protection for stroke patients; however, it mentions neither CGRP nor CGRP antagonism. Meanwhile, the Szeto literature review references CGRP only in passing to state that as one of several vasodilators, CGRP increases K_{ATP} channel activity. But the literature review does not otherwise opine on the role of CGRP. And Warner does not explain how such a singular, tangential reference would constitute any type of "data," "new analyses," or "event[]" that we can consider as newly acquired information. 21 C.F.R. §§ 601.12(f)(6). Nor does Warner provide us with an explanation that would allow us to reasonably infer that these literature reviews present risks not previously considered by the FDA. Without more, we do not consider these articles newly acquired information for purposes of this appeal.

¹⁴ See Jing-Jing Zhao et al., Remote Ischemic Postconditioning for Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, 131 Chinese Med. J. 956 (2018).

¹⁵ See Vivian Szeto et al., The Role of KATP Channels in Cerebral Ischemic Stroke and Diabetes, 39 Acta Pharmacologica Sinica 683 (2018).

That leaves us with seven articles. We can also dispose of the 2012 Kokkoris literature review¹⁶ as not constituting newly acquired information for purposes of this appeal. That review discusses some possible neuroprotective mechanisms of CGRP during subarachnoid hemorrhage.¹⁷ However, the FDA specifically reviewed a study finding that "elevated CGRP levels may prevent focal cerebral ischemia following subarachnoid hemorrhage." Like the district court, we therefore lack any basis for determining that this article "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." Warner, 2025 WL 490720, at *10 (citation modified).

This leaves us with six articles, including the 2018 Guo study,¹⁸ which administered a CGRP antagonist to rats undergoing myocardial ischemia. That study found that CGRP influences myocardial infarct size and "may protect [such] cardiomyocytes via homeostasis of mitochondrial function." But, as we discuss in

¹⁶ See Stelios Kokkoris et al., Role of Calcitonin Gene-Related Peptide in Cerebral Vasospasm, and As a Therapeutic Approach to Subarachnoid Hemorrhage, 3 *Frontiers Endocrinology* 135 (2012).

¹⁷ A subarachnoid hemorrhage is a bleed within the subarachnoid space, which lies between two of the three membranes that cover the central nervous system. See Subarachnoid Hemorrhage, *Stedman's Medical Dictionary*, *supra*, at 873; Arachnoid Mater, *Stedman's Medical Dictionary*, *supra*, at 127.

¹⁸ See Zheng Guo et al., Independent Roles of CGRP in Cardioprotection and Hemodynamic Regulation in Ischemic Postconditioning, 828 *Eur. J. Pharmacology* 18 (2018).

section III.B.3 of this opinion, a manufacturer cannot employ the CBE procedure to change the warnings or precautions on a label without also meeting the causal association standard set forth in 21 C.F.R. § 201.57(c). Warner does not address how the study's findings -- pertaining only to the effects of CGRP on the mitochondrial membrane as it relates to cells in the heart, rather than the brain -- would have any causal relationship with the cerebral outcomes suffered by Lucas. So we need not address it any further.

The 2018 Basalay literature review¹⁹ discusses the neuroprotective qualities of remote ischemic conditioning²⁰ and suggests that the mechanisms of ischemic conditioning may differ between the heart and brain. The review makes only passing reference to CGRP's function in the brain. But the FDA at multiple points considered the theoretical concern of CGRP antagonism and

¹⁹ See Marina V. Basalay et al., Neural Mechanisms in Remote Ischaemic Conditioning in the Heart and Brain: Mechanistic and Translational Aspects, 113 Basic Resch. Cardiology 25 (2018).

²⁰ Ischemia is the "[l]ocal loss of blood supply due to a mechanical obstruction . . . of the blood vessel." Ischemia, Stedman's Medical Dictionary, supra, at 1001. As the district court explained, "[i]schemic conditioning involves intentionally exposing tissue or organs to brief periods of ischemia (i.e., reduced blood flow and oxygenation), followed by reperfusion (i.e., restoration of blood flow to the tissue or organ), to protect against organ damage following a major ischemic event, such as a heart attack or stroke." Warner, 2025 WL 490720, at *9.

its "potential . . . to adversely impact the beneficial effects of ischemic preconditioning," including in reviews by the Division of Neurology Products and the Division of Cardiovascular and Renal Products. Indeed, the DNP noted that "[t]here are numerous publications on preconditioning and its potential beneficial effects, not only on the cardiovascular system," but also on the "neurological" system. Citing in part to a publication concerning the neuroprotective effects of ischemic preconditioning, the DNP noted that "[s]everal publications . . . point out that multiple endogenous factors may be involved in the complex process(es) underlying the phenomenon and the current limited understanding of the role of any one of these factors, including CGRP." In light of these considerations by the FDA, we are certain that the Basalay literature review does not plausibly "reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." 21 C.F.R. §§ 601.12(f)(6), 314.3(b).

The 2007 Rehni study²¹ presents a close call. This study found that the administration of a CGRP antagonist to mice "attenuated" "the neuroprotective effect of remote mesenteric ischaemic preconditioning."²² As we explained regarding the 2018

²¹ See Ashish K. Rehni et al., Possible Involvement of Insulin, Endogenous Opioids and Calcitonin Gene-Related Peptide in Remote Ischaemic Preconditioning of Brain, 127 Pharm. Soc'y of Japan 1013 (2007).

²² Rehni noted that cerebral ischemia in particular "has been reported to impair short-term memory" and "sensorimotor ability."

Basalay review, the FDA was well-aware of the "theoretical concern" of CGRP antagonism and its "potential . . . to adversely impact the beneficial effects of ischemic preconditioning." But the Rehni study -- at least on this record -- arguably took a step further by reporting that the introduction of a CGRP receptor antagonist "abolished the neuroprotection afforded by remote mesenteric ischaemic preconditioning." According to the study, "it may be concluded that remote mesenteric ischaemic preconditioning exerts neuroprotective effect possibly[] mediated through the release of . . . [CGRP] with consequent activation of [its] receptors." On this record and given the generous pleading standard, we cannot be certain that the Rehni study's findings do not plausibly "reveal risks of . . . a greater severity . . . than previously included in submissions to [the] FDA." 21 C.F.R. § 601.12(f)(6).

That leaves three articles concerning the interactions between CGRP and the blood-brain barrier.²³ In the first, the 2011

However, "remote mesenteric ischaemic preconditioning has been observed to prevent ischaemia" and has also prevented an "increase in cerebral infarct size, impairment of short-term memory, [and] motor incoordination."

²³ As further defined by the Sorby-Adams literature review presented by Warner, the blood-brain barrier is a "semi-permeable barrier existing between the brain and blood" that is composed of "endothelial cells with tight junctions (TJ), adherens junctions, astrocytes, pericytes, and the basement membrane," which, together, assist in the barrier's functions of "supplying the brain with essential nutrients such as oxygen and glucose, mediating the efflux of waste products, and facilitating the movement of

Liu study,²⁴ researchers placed rats under stroke conditions and administered CGRP to one group and saline solution to the other. The findings suggest that the effects of blood-brain barrier disruption in the study's rats were not short-lived: "[Blood-brain barrier] leakage after ischemia-reperfusion injury in the rat was continuous and long-lasting, without any closure up to several weeks." The authors found that "CGRP administration could reduce" the permeability of the blood-brain barrier and that it "might protect against [blood-brain barrier] disruption after brain ischemia reperfusion injury by improving the damage of capillary endothelium cells and enhancing basal membrane."

The second of these articles is the 2017 Sorby-Adams literature review²⁵ -- published three months after Aimovig's BLA submission.²⁶ This review concerns blood-brain barrier disruption

nutrients and plasma proteins." See Annabel J. Sorby-Adams et al., The Role of Neurogenic Inflammation in Blood-Brain Barrier Disruption and Development of Cerebral Oedema Following Acute Central Nervous System (CNS) Injury, 18 Int'l J. Molecular Sci. 1788 (2017).

²⁴ See Zhen Liu et al., Calcitonin Gene-Related Peptide Prevents Blood-Brain Barrier Injury and Brain Edema Induced by Focal Cerebral Ischemia Reperfusion, 171 Regul. Peptides 19 (2011).

²⁵ See Sorby-Adams et al., supra.

²⁶ The FDA approved Amgen's BLA for Aimovig in May 2018. Only the Basalay article was published after that approval. Indeed, five of the articles -- the Zhai, Sorby-Adams, Zhao, Szeto, and Guo articles -- were published in the year between Amgen's BLA submission on May 17, 2017 and the FDA's ultimate approval of the label on May 17, 2018. And the Rehni, Liu, and Kokkoris articles

following traumatic brain injury (TBI) or stroke. The review cites, among other studies, the 2011 Liu study and emphasizes that "CGRP administered at the onset of reperfusion produced a significant reduction in infarct volume, [blood-brain barrier] permeability and cerebral oedema following rodent stroke," suggesting that CGRP plays a role in stabilizing the blood-brain barrier. The review also discusses how CGRP is involved in angiogenesis, or the development of new blood vessels. See Angiogenesis, Stedman's Medical Dictionary 86 (28th ed. 2006).

The third of these articles, the 2018 Zhai study,²⁷ was published nearly a year after Aimovig's BLA submission and only one month before the FDA's approval of the Aimovig label. In this study, researchers compared "CGRP knockout mice" -- mice genetically modified to no longer produce CGRP -- with wild mice that were administered human CGRP. Researchers then placed the two groups under conditions of cerebral ischemia by blocking blood flow in the external carotid artery. The study's findings indicate that mice that could not produce CGRP exhibited "increased blood-brain barrier damage-related factors," suggesting that "CGRP deficiency leads to greater [blood-brain barrier] damage during

were all published prior to the submission of Aimovig's BLA.

²⁷ See Liuyu Zhai et al., Endogenous Calcitonin Gene-Related Peptide Suppresses Ischemic Brain Injuries and Progression of Cognitive Decline, 36 J. Hypertension 876 (2018).

chronic cerebral ischemia." And "[t]he mechanisms underlying hypoxic-ischemic brain damage include death of neuronal and glial cells and loss of integrity of the blood-brain barrier." The authors noted that "[s]tudies have shown there is a significant association between [blood-brain barrier] dysfunction and vascular cognitive impairment." Thus, cognitive disorder "may be in part attributable to damage to the [blood-brain barrier]." As a result of not being able to produce CGRP, the knockout mice also suffered from "more extensive neuronal cell damage"; "more extensive irreversible cell damage";²⁸ "delayed recovery of cerebral blood flow"; higher levels of "demyelination"²⁹ and "astrocyte activation";³⁰ a reduction in "compensative capillary formation";

²⁸ The study also found that CGRP-deficient mice had "significantly increased expression of adrenomedullin in the cerebral cortex," which "may reflect compensation for the CGRP deficiency," though we do not find that the study concluded that such possible compensation outweighed or prevented the irreversible cell damage.

²⁹ Demyelination is the "[l]oss of myelin, with preservation of the axons or fiber tracts." Demyelination, Stedman's Medical Dictionary, supra, at 509. The myelin sheath is an "envelope" that "surround[s] most axons," Myelin Sheath, Stedman's Medical Dictionary, supra, at 1758-59, which are the parts of nerve cells that "conduct[] nervous impulses away from the cell body," Axon, Stedman's Medical Dictionary, supra, at 191.

³⁰ An astrocyte is "[o]ne of the large neuroglia cells of nervous tissue." Astrocyte, Stedman's Medical Dictionary, supra, at 171. Neuroglia are "[n]onneuronal cellular elements of the central and peripheral nervous system" that have "important metabolic functions" because they are "invariably interposed between neurons and the blood vessels supplying the nervous system." Neuroglia, Stedman's Medical Dictionary, supra, at 1310.

and "more severe disturbance of memory." The authors concluded that, in addition to stabilizing the blood-brain barrier, "CGRP may also suppress inflammation and oxidative stress, promote angiogenesis and exert a direct antiapoptotic effect."³¹

The district court found that none of these four articles constituted newly acquired information. As to the Rehni and Liu studies, the district court concluded that "[t]he DCRP [had] reviewed 'the world's literature' before preparing its report on the theoretical risks associated with CGRP antagonism," and so "[i]t is not plausible that articles bearing on that subject, published at least four years before the DCRP began preparing its report, 'reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.'" Warner, 2025 WL 490720, at *10. The district court also concluded that the Sorby-Adams literature review could not plausibly constitute newly acquired information because that review relied upon the Liu study. Id. As to the 2018 Zhai study, the district court found this study "too attenuated from Warner's claim to plausibly constitute newly acquired information." Id. at *11. As part of its reasoning, the district court determined that "the study does not address whether its findings about mice with a CGRP deficiency generalize to drugs, like Aimovig, that are CGRP

³¹ Apoptosis is the process of "[p]rogrammed cell death." Apoptosis, Stedman's Medical Dictionary, supra, at 121.

antagonists" and that Warner had not cited, nor had the court uncovered, "any precedent for treating a single animal study not involving the manufacturer's drug as newly acquired information." Id.

We are inclined to read the record as the district court did. But at the same time -- and without the benefit of any expert testimony -- we find that inclination falls short of allowing us to conclude with certainty that the CBE procedure would have failed. See Burt, 84 F.4th at 50 (requiring an affirmative defense be "establish[ed] . . . with certitude" in order to uphold a court's grant of a motion to dismiss based on that defense (citation modified)).

For example, we are not convinced by the district court's assumption that the FDA must have reviewed the Rehni and Liu studies as part of its review of the "world's literature." The FDA's review of the "world's literature" was limited to "published evidence concerning a theoretical risk conferred by [CGRP] antagonism via any mechanism of worsened ischemia due to impairment of compensatory vasodilation in the setting of ischemic vascular events." Nothing in the record suggests that the FDA reviewed the "world's literature" concerning the possible role of CGRP's effect on the blood-brain barrier or its possible neuroprotective effects outside of vasodilation -- or, for that matter, the "attenuat[ing]" impact of CGRP antagonism as it relates to the neuroprotective

effects of ischemic preconditioning.³² We also find no evidence in the record as it now stands that the Rehni study, Liu study, Zhai study, or the Sorby-Adams literature review were brought to the FDA's attention. Nor does Amgen point us toward any analysis by the FDA of CGRP's effect on the blood-brain barrier in the setting of cerebral injury.³³ At this stage in the proceedings, we cannot draw a determinative inference against Warner that the FDA's world-literature review included studies on CGRP's role in protecting or stabilizing the blood-brain barrier when Amgen itself points to no language or analysis from the FDA suggesting as much.

Contrary to Amgen's assertions, the publication dates of these articles are also not dispositive of whether a study

³² This is not to say that the FDA was not at all aware of some possible neuroprotective effects of CGRP in the setting of cerebral injury. Indeed, and as we noted previously, the FDA had cited to a study regarding the possible protective effects of elevated CGRP levels following subarachnoid hemorrhage. But Amgen does not reference this study in its briefing or provide the study in the record for our review. Without anything more, we cannot assess whether this study relates to neuroprotective effects of CGRP outside of its vasodilatory role. Such technical matters serve as a reminder that at this stage in the proceedings, our role is not to determine whether the studies and articles submitted by Warner constitute newly acquired information; rather, we ask only whether we can say with certitude that they do not.

³³ Indeed, as Aimovig had only been studied in healthy populations without such histories, the FDA was under the impression that only a "very small fraction" of Aimovig could cross the blood-brain barrier. This reference was included in passing and only as a reason for the Controlled Substance Staff at the FDA declining to review Aimovig's BLA submission.

constitutes newly acquired information. A study published prior to the approval of a drug or biologic's label may still qualify as newly acquired information if it had not been "previously submitted" to the FDA. Celexa, 779 F.3d at 42 (quoting 21 C.F.R. § 314.3(b)); see also 21 C.F.R. § 601.12(f)(6) (parallel regulation for biologics). And, as the Supreme Court has stated, newly acquired information "also encompasses 'new analyses of previously submitted data'" to "account[] 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." Wyeth, 555 U.S. at 569 (quoting Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49604).

Nor are we certain that the Zhai study fails to qualify as newly acquired information because the article does not discuss whether its findings of CGRP deficiency in mice can be generalized to CGRP antagonism in humans. Although labeling requirements for human prescription drugs and biologic products provide that "[t]he labeling must be based whenever possible on data derived from human experience," conclusions based on "animal data" that are "necessary for safe and effective use of the drug in humans must [also] be identified as such and included with human data in the appropriate section of the labeling." 21 C.F.R. § 201.56(a)(3). Indeed, the parties agree that "FDA guidance permits theoretical

warnings 'if the animal data raises substantial concern about the potential for . . . adverse reaction in humans.'" As Aimovig was the first drug of its kind to be reviewed by the FDA, the FDA relied largely on animal studies, including studies on canines and rats. And the FDA did not restrict its review of studies to those administering Aimovig or a similar CGRP antagonist. For example, when the FDA considered the "world's literature," it reviewed two canine studies where "[n]o [CGRP] antagonist was administered." The FDA also considered rat studies, including a study on diabetic rat hearts where researchers did not administer a CGRP antagonist, as well as studies discussing the use of CGRP knockout mice. We see no clear reason why we should certainly exclude animal studies related to CGRP in our assessment of newly acquired information if the FDA did not do the same.

Viewed together, the Rehni study, the Liu study, the Sorby-Adams literature review, and the Zhai study plausibly suggest risks of CGRP antagonism outside of its effect in regulating blood flow in the body. The Rehni study seems to indicate that the neuroprotective effects of ischemic preconditioning may be "attenuated" or "abolished" by a CGRP antagonist. Meanwhile, the Liu, Sorby-Adams, and Zhai articles seem to indicate that CGRP deficiency is related to greater blood-brain barrier damage in the setting of cerebral injury as well as irreversible cell death in the brain and disturbances in memory.

Based on the record before us, we cannot say with certitude that Warner has failed to plausibly allege a "reasonable basis" to view the articles by Rehni, Liu, Zhai, and Sorby-Adams collectively as "reveal[ing] risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." Zofran, 57 F.4th at 337 (quoting 21 C.F.R. § 314.3(b)); see also 21 C.F.R. § 601.12(f)(6) (parallel regulation for biologics).

2.

We turn now to the second prong of our CBE inquiry, which requires Warner to allege facts plausibly showing a reasonable basis for establishing that the proposed change is "for the purpose of accomplishing" one of five permissible objectives under the CBE procedure.³⁴ Celexa, 779 F.3d at 37. Our discussion here is

³⁴ A manufacturer may use the CBE procedure to supplement a label "to accomplish any of the following":

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about abuse, dependence, psychological effect, or overdose;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product; and

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

brief, as the parties do not dispute that Warner's proposed changes if adopted would serve "[t]o add or strengthen" a "warning, precaution, or adverse reaction" on Aimovig's label. 21 C.F.R. § 601.12(f)(2)(i)(A). "Warnings and precautions" include "clinically significant adverse reactions," as well as "potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions)." Id. § 201.57(c)(6)(i). Meanwhile, an "adverse reaction" is defined as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." Id. § 201.57(c)(7) (emphases added). At this stage in the proceedings, based on the facts presented by Warner in the Liu, Sorby-Adams, and Zhai articles, we cannot say with certainty that the labeling changes Warner proposes would not serve the purpose of "add[ing] or strengthen[ing]" the "warning[s], precaution[s], or adverse reaction[s]" on Aimovig's label. Id. § 601.12(f)(2)(i)(A).

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the product that FDA specifically requests be submitted under this provision.

21 C.F.R. § 601.12(f)(2)(i)(A)-(E).

3.

Finally, we turn to the issue of causal association. We similarly treat this issue as a question of law based on the record as it now stands, noting that many of the factual questions in our preemption analysis are "subsumed within an already tightly circumscribed legal analysis." Albrecht, 587 U.S. at 317.

Both the "warnings and precautions" and "adverse reactions" sections of a label have their own distinct causal association requirements. For "warnings and precautions," a manufacturer "must" revise the label "as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. § 201.57(c)(6)(i) (emphasis added). On the other hand, to add an adverse reaction to the label, the manufacturer need only have "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." Id. § 201.57(c)(7) (emphasis added). But in either context, the requirement of a causal association is not "intended to suggest that there is a mathematically precise distinction between whether there is, or is not, sufficient evidence of a causal relation between a drug and an adverse effect." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49604. Indeed, because "causation need not have been 'definitely established' for a

warning to be required," the "standard [can] be met by a wide range of evidence." Id. (quoting 21 C.F.R. § 201.57(c)(6)(i)).

Because the district court hinged its futility finding primarily on its conclusion that the articles Warner provided did not constitute newly acquired information, it understandably dedicated only a few sentences to the causal association prong of the analysis, declaring that "none of the articles link Aimovig or any other CGRP-blocking drug to an adverse event or risk." Warner, 2025 WL 490720, at *9. On appeal, the parties disagree as to the specific causal association required in this case. Amgen suggests that Warner must show a "plausible connection between Aimovig and an increased risk of seizures in people with an AVM or a history of seizures" like Lucas. Warner insists she "does not need . . . to show that Aimovig was associated with an increased risk of seizures." Rather, she asserts that the newly acquired information "establishes that Aimovig contributed to triggering or worsening the effects of Lucas's seizure by, for example, weakening his blood-brain barrier," and thus "[s]he need only allege Aimovig's association with damage that Lucas experienced, such as worsened outcomes following cerebral injury."³⁵ (Emphasis added).

³⁵ At oral argument, Amgen contended that Warner's theory was premised only on Aimovig causing seizures, and thus Warner had waived any claim "that CGRP was somehow protective and that protective ability was lost from taking Aimovig." We disagree. At the motion hearing before the district court, Warner argued that "evidence in the record" explained "that part of Lucas's

We agree with Warner. At this stage in the proceedings, expert testimony has not yet established the exact causal chain between CGRP inhibition and each symptom suffered by Lucas. And because "precise knowledge of the chain of events . . . may often be unavailable to a plaintiff" at the motion to dismiss stage, "we take to heart the Supreme Court's call to 'draw on our judicial experience and common sense as we make a contextual judgment about the sufficiency of the pleadings.'" Fortuño-Burset, 640 F.3d at 16 (quoting Sanchez v. Pereira-Castillo, 590 F.3d 31, 48 (1st Cir. 2009)). In making that judgment based on the record as it now stands, we are simply not certain that there is no causal relationship between Aimovig and the extent of the injuries Lucas experienced.

We are also not convinced by Amgen's argument that the studies "do not discuss Aimovig" and thus cannot satisfy the causal association standard. We do not read the regulations defining warnings and precautions under 21 C.F.R. § 201.57(c)(6)(i) and adverse reactions under § 201.57(c)(7) to be so restrictive.

injury was that the drug might have crossed the blood-brain barrier." This was consistent with scientific studies, claimed Warner, regarding how "the activation of CGRP in the brain . . . protects the blood-brain barrier and . . . protects the brain from the effects of stroke." And in her motion for leave to amend her complaint, Warner again provided that the articles she submitted constituted newly acquired information that "illuminated cerebral risks not considered by the FDA," including that CGRP "helps stabilize the blood-brain barrier" and that "[b]locking CGRP risks disrupting this protective mechanism."

Those regulations define an adverse reaction as an "undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." Id. § 201.57(c)(7). Nothing in this definition requires that the inclusion of an adverse reaction in labeling be based solely on clinical studies of the drug itself. And FDA guidance documents provide that "[t]here are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur." FDA, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products -- Content and Format 5 (2011), <https://www.fda.gov/media/71866/download> [<https://perma.cc/634T-UDZE>].³⁶ That guidance further instructs that the Warnings and Precautions section of a drug label should include "anticipated" adverse reactions if "[i]t appears likely that the adverse reaction will occur with the drug based on what is known about the pharmacology, chemistry, or class of the drug" or if "[a]nimal data raises substantial concern about the potential for occurrence

³⁶ These documents, though not binding, accord with our reading of the regulations regarding biologic labeling and the pertinent definitions of "warnings and precautions" and "adverse reactions" under those regulations. We also reject Amgen's argument that Warner waived reliance on this guidance by not citing it in her supplemental brief to the district court, which was limited to five pages in length at the court's direction.

of the adverse reaction in humans." Id. This guidance is relevant to our analysis of the facts in this case. As we have previously stated, Aimovig was the first drug of its kind to be approved or even reviewed by the FDA, and, as such, the FDA reviewed multiple animal studies that did not involve the administration of Aimovig or even a CGRP antagonist to study the pertinent risks of the drug. We decline to read into the regulations a more restrictive lens than that required by FDA guidance and the FDA's own review of the biologic in this case.

In the setting of cerebral ischemia, the four articles submitted by Warner can be read as finding an association between CGRP antagonism and the dilution of neuroprotective effects from ischemic conditioning, as well as a relationship between CGRP inhibition and an increase in blood-brain barrier permeability, irreversible cell death, and damage to memory function. Based on these studies, Warner posits that blocking CGRP in patients with Lucas's history would be causally associated with a greater risk of cerebral harm in situations "where CGRP response could be protective." And, because the blood-brain barrier may be damaged in the setting of cerebral injury under conditions such as stroke, Warner argues that her submitted articles "suggest[] that blocking CGRP could accelerate the death of oxidatively stressed neurons in a variety of neurological emergencies, raising concern that

patients on a CGRP-blocker could face more disastrous outcomes in the settings of brain injury."

Based on the foregoing and as the record now stands, we are not certain that the Rehni, Liu, Sorby-Adams, and Zhai articles do not present "reasonable evidence of a causal association" or, alternatively, "some basis to believe there is a causal relationship" between Aimovig and worsened outcomes in cases of cerebral injury in individuals with a history of seizure or cerebrovascular disease such as Lucas. See 21 C.F.R. § 201.57(c)(6)(i), (c)(7). This satisfies the causal association prong of our inquiry into Amgen's affirmative defense at this stage of the case.

4.

Even given the foregoing, Amgen would still prevail in its preemption defense if there was "clear evidence" that, had it been informed of the three studies discussed above, the FDA would still have rejected the label change that Warner says state tort law required. See Zofran, 57 F.4th at 342. At this early stage of the proceedings, however, Amgen has chosen not to rely on such an argument to sustain the court's Rule 15(a) futility determination regarding Warner's request to amend her complaint. Nor did the district court. We conclude that Warner's proposed amendment -- as limited to the four articles that Amgen has failed to conclusively establish do not plausibly constitute newly

acquired information -- would not have been futile. We therefore do not consider the merits of this reserved defense.

IV.

For the foregoing reasons, we reverse the district court's rejection of Warner's request to amend her complaint -- but only to the limited extent that Warner asserts a claim that the Rehni, Liu, Sorby-Adams, and Zhai articles enabled Amgen to use the CBE procedure to amend its approved label to reflect a concern that Aimovig could reduce the protective mechanisms of CGRP in the cerebral system in the setting of cerebral injury. The district court's rulings are otherwise affirmed, and this case is remanded for further proceedings consistent with this opinion. We award no costs to either party.