United States Court of Appeals
For the First Circuit

No. 17-2066

ROBERT GUSTAVSEN; JOSEPH CUGINI; DEMETRA COHEN; JACKIE CORBIN; LEE WILBURN; MARY LAW; CECILIA BRATHWAITE,

Plaintiffs, Appellants,

v.

ALCON LABORATORIES, INC.; ALCON RESEARCH, LTD.; FALCON PHARMACEUTICALS, LTD.; SANDOZ, INC.; ALLERGAN, INC.; ALLERGAN USA, INC.; ALLERGAN SALES, LLC; PFIZER, INC.; VALEANT PHARMACEUTICALS INTERNATIONAL, INC.; BAUSCH AND LOMB, INC.; ATON PHARMA, INC.; MERCK & CO., INC.; MERCK, SHARP & DOHME (I.A.) CORP.; PRASCO, LLC; AKORN, INC.,

Defendants, Appellees.

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

[Hon. Mark L. Wolf, Senior U.S. District Judge]

Before

Thompson, Kayatta, and Barron,
Circuit Judges.

Leah M. Nicholls, with whom Public Justice, P.C., Richard S. Cornfeld, Law Office of Richard S. Cornfeld, John C. Simon, Kevin M. Carnie, Jr., The Simon Law Firm, P.C., Kenneth J. DeMoura, DeMoura Smith LLP, Emily Lisa Perini, Perini-Hegarty & Associates, P.C., and Brian Wolfman were on brief, for appellants.

Gregory E. Ostfeld, with whom David G. Thomas, Michael Pastore, Christiana Jacxsens, Greenberg Taurig, LLP, Peter Simshauser, Skadden, Arps, Slate, Meagher & Flom LLP, Robyn E. Bladow, Austin Norris, Kirkland & Ellis LLP, Joseph P. Crimmins,

Posternak Blankstein & Lund LLP, John M. Kilroy, Jr., J. Santon Hill, Polsinelli PC, W. Scott O'Connell, Nixon Peadoby LLP, James P. Muehlberger, Lori A. McGroder, Shook, Hardy & Bacon LLP, Stephen G. Strauss, Bryan Cave LLP, David J. Volkin, Law Offices of David J. Volkin, David B. Chaffin, and White and Williams LLP were on brief, for appellees.

Jeffrey S. Bucholz, Paul Alessio Mezzina, King & Spalding LLP, Peter Tolsdorf, and Manufacturers' Center for Legal Action, on brief for American Tort Reform Association, The Chamber of Commerce of the United States of America, The National Association of Manufacturers, and Pharmaceutical Research & Manufacturers of America, amici curiae.

David R. Geiger, Kristyn M. DeFillip, and Foley Hoag LLP, on brief for Product Liability Advisory Council, Inc., amicus curiae.

August 27, 2018

KAYATTA, **Circuit Judge**. Our disposition of the merits of this appeal turns on a single question: Can manufacturers of prescription eye drops change the medication's bottle so as to alter the amount of medication dispensed into the eye without first getting the FDA's approval? Finding that federal law requires prior approval for such a change, we hold that state law claims challenging the manufacturers' refusal to make this change are preempted. Our reasoning follows.

I.

Because this appeal comes to us following the district court's grant of a motion to dismiss, we draw the facts from the operative complaint. SEC v. Tambone, 597 F.3d 436, 438 (1st Cir. 2010) (en banc).

Defendants in this case are companies engaged in the manufacturing, marketing, and distribution of both brand name and generic prescription eye drops. These drops treat a multitude of ailments, including glaucoma, allergies, infections, inflammation, and pre- and post-operative conditions. The eye drop solutions are sold in plastic bottles shaped at one end to form a plastic dispenser. To use the eye solution, consumers must squeeze or tap the bottle, emitting a drop of solution directly into the eye. Consumers cannot dispense less than one drop at a time. And the dimensions of the bottle's dispenser, rather than any factor under human control, determine the size of each drop. Specifically, the

complaint explains, the volume of the drop dispensed varies based on the "inner diameter or hole and the outer diameter of the tip" of the dispenser. The bottles do not disclose the size of the eye drops, nor do they reveal an estimate of the number of drops or doses contained in each bottle.

Plaintiffs complain that defendants deliberately designed their dispensers to emit unnecessarily large drops, on the order of 24 to 52 microliters. This ploy, plaintiffs say, forces patients to waste medication, to their detriment and to defendants' gain. Plaintiffs marshal a body of scientific literature to support their argument. The scientific consensus, they say, is that the optimal size of drops rests between 5 and 15 microliters. The reason is a matter of human anatomy. The fornix, which is the area between the eye and the lower eyelid, is only capable of absorbing a small portion of the unnecessarily large drops dispensed by defendants' bottles.

All manufacturers of prescription eye drops, plaintiffs say, engage in this practice; there is no prescription eye solution on the market that dispenses drops that are not substantially larger than 15 microliters. Plaintiffs do not allege, however, that this industry standard is the result of conspiracy, or that defendants otherwise acted in concert. Rather, they allege that defendants "separately engaged in" the challenged conduct. And that conduct, plaintiffs allege, harms patients in two ways.

First, it costs patients money. If the bottles dispensed smaller drops, then each bottle would deliver more doses, and patients would be able to purchase fewer bottles over any set amount of time. By comparing the number of bottles a patient would use if the bottles dispensed 15 microliter doses against the number of bottles each patient is now required to purchase, plaintiffs calculate that a patient, on a yearly basis, could save upwards of $500, depending on the brand and type of solution used.

These calculations naturally rely on an assumption that a manufacturer would not substantially increase the price of a bottle that dispensed smaller drops. Support for this assumption in the complaint comes in two forms. Plaintiffs point out that defendants currently price the various sized bottles proportionate to their volume. A bottle twice the size costs approximately twice as much. The inference they would have us draw is that, if only the drop size were to change but the volume of solution in the bottle were to stay consistent, the price of the bottle would stay constant too. Plaintiffs also point to various statements in academic studies that draw a connection between the drop size and cost to plaintiffs. For example, in a study published by Allergen (one of the defendants here), the authors say that "a smaller drop size would mean that more doses could be dispensed from each bottle of medication, providing cost savings to patients and managed care providers." They also allege that, following a study by scientists

employed by Alcon (another defendant here) that concluded that 16 microliter drops were as effective as 30 microliter drops, Alcon's top marketing executive said that Alcon would not make the change to its bottles because "patients would use the bottles longer and Alcon would therefore sell less product and make less money."

The second alleged impact on patients is physical. Excess eye drops that stream down the cheek can cause allergies and pigmentation. The excess drops that enter the bloodstream do so without first going through metabolic inactivation in the liver. And without the liver's processes, say plaintiffs, the eye solution can lead to decreased cardiovascular response to exercise, lowered blood pressure, and emotional and psychiatric side effects. Although plaintiffs allege an increased risk of these consequences, they do not allege that any named plaintiff did, in fact, experience any such side effect.

Armed with these grievances, the named plaintiffs filed suit in federal court on their own behalf and on behalf of a putative class of prescription eye solution purchasers. The named plaintiffs are residents of either Massachusetts or New York who purchased eye solution from at least one of the defendant manufacturers during the four years preceding the filing of their lawsuit. They allege two categories of violations.

First, they allege that defendants' practice is "unfair" under Massachusetts state law and the laws of twenty-five other states and the District of Columbia, all of which adopt the meaning of "unfair" as applied in section 5 of the Federal Trade Commission Act. 15 U.S.C. § 45(a)(1). Plaintiffs do not allege that defendants' actions are deceptive.

Second, under the laws of New York and sixteen other states, plaintiffs allege claims for unjust enrichment and for "money had and received." The basis for these latter two causes of action is plaintiffs' contention that defendants received excess profits from their actions to which they are not entitled.

All defendants moved to dismiss. They asserted first that the court lacked subject-matter jurisdiction because plaintiffs had failed to satisfy the "injury in fact" requirement of Article III standing. Second, defendants argued that plaintiffs' claims were preempted by Food and Drug Administration regulations. Specifically, they contended that changing the dispensers to reduce the size of the eye drops -- the change plaintiffs claim state law mandates -- requires pre-approval from the FDA, thus implicating the doctrine of impossibility preemption. Third, defendants argued that plaintiffs failed to state a claim under the state laws pleaded.[1]

[1] For the sake of simplicity, we mention only the grounds for defendants' motion that they repeat on appeal.

Citing In re Pharmaceutical Industry Average Wholesale Price Litigation, 582 F.3d 156, 190-91 (1st Cir. 2009), the district court ruled that plaintiffs' "plausible claim that they've overpaid for the defendants' eyedrops," alleged a "cognizable form of injury for standing purposes." The district court nevertheless dismissed the complaint without ruling on the merits of the claims under state laws, finding that the FDA regulations preempted plaintiffs' suit. See Gustavsen v. Alcon Labs., Inc., 272 F. Supp. 3d 241, 250 (D. Mass. 2017). In so doing, the court relied on a section of an FDA regulation that categorized changes "that may affect . . . drug product sterility assurance" as major changes requiring FDA approval prior to implementation. Id. at 251; 21 C.F.R. § 314.70(b)(2)(iii). Plaintiffs now appeal.

II.

Because Article III standing implicates our ability to hear a case, see Baena v. KPMG LLP, 453 F.3d 1, 4 (1st Cir. 2006), we begin with defendants' contention that plaintiffs fail to satisfy the injury in fact requirement of Article III standing. Our review is de novo. Hochendoner v. Genzyme Corp., 823 F.3d 724, 730 (1st Cir. 2016).

Article III of the Constitution limits the judicial power of the federal courts to "Cases" and "Controversies." U.S. Const. art. III, § 2. Such a case or controversy exists only when

the plaintiff demonstrates "such a personal stake in the outcome of the controversy as to assure that concrete adverseness which sharpens the presentation of issues upon which the court so largely depends." Katz v. Pershing, LLC, 672 F.3d 64, 71 (1st Cir. 2012) (quoting Baker v. Carr, 369 U.S. 186, 204 (1962)). To demonstrate a "personal stake" necessary to invoke the jurisdiction of the federal courts, a plaintiff must satisfy the familiar triad of injury in fact, causation, and redressability. Lujan v. Defs. of Wildlife, 504 U.S. 555, 560-61 (1992).

Plaintiffs bear the burden of establishing standing. See Lujan, 504 U.S. at 561; Hochendoner, 823 F.3d at 730. The manner in which plaintiffs must make these showings varies with "the manner and degree of evidence required at the successive stages of the litigation." Lujan, 504 U.S. at 561. Thus, at the motion to dismiss stage, we apply the same plausibility standard used to evaluate a motion under Rule 12(b)(6). See Hochendoner, 823 F.3d at 731. We first "accept as true all well-pleaded factual averments in the plaintiff's . . . complaint and indulge all reasonable inferences therefrom in his favor." Katz, 672 F.3d at 70-71 (quoting Deniz v. Mun'y of Guaynabo, 285 F.3d 142, 144 (1st Cir. 2002)). We then ask whether the plaintiff has pleaded "sufficient factual matter to plausibly demonstrate his standing to bring the action." Hochendoner, 823 F.3d at 731. Because this appeal comes to us before any class is certified, we evaluate only

whether the named plaintiffs have standing to pursue their own claims. Katz, 672 F.3d at 71.

With this general framework in mind, we begin with the question of whether the complaint adequately alleges injury in fact. The injury in fact requirement is, itself, composed of several prongs. A constitutionally sufficient injury arises from an "invasion of a legally protected interest" that is both "concrete and particularized" as well as "actual or imminent," rather than "conjectural or hypothetical." Lujan, 504 U.S. at 560 (internal quotation marks omitted); see also Spokeo, Inc. v. Robins, 136 S. Ct. 1540, 1545 (2016) (clarifying that "concrete" and "particularized" constitute independent, necessary requirements for standing).

The injury alleged here takes the form of an out-of-pocket loss of $500 to $1000 per year.[2] This alleged loss passes muster under each of these prongs. Certainly plaintiffs have a legally protected interest in their own money. See Cent. Az. Water Conservation Dist. v. EPA, 990 F.2d 1531, 1537 (9th Cir. 1993) (noting that "pecuniary or economic injury is generally a legally protected interest"). Nor do defendants argue otherwise.

[2] A careful reader will also remember that plaintiffs alleged an increased risk of certain physical side effects. But plaintiffs do not press that allegation as a basis for standing. See Kerin v. Titeflex Corp., 770 F.3d 978, 979 (1st Cir. 2014) (identifying the situations in which increased risk of harm can be a cognizable injury for standing).

We also have no trouble concluding that the injury is particularized. Here, we are concerned with whether a plaintiff has been affected "in a personal and individual way." Spokeo, 136 S. Ct. at 1548 (quoting Lujan, 504 U.S. at 560 n.1). An out-of-pocket loss of money satisfies the requirement of particularization because it constitutes undisputed harm to the plaintiff specifically. See Katz, 672 F.3d at 71 ("Particularity demands that a plaintiff must have personally suffered some harm.").

The injury as alleged is also concrete. Like the requirement of a "legally protected interest," concreteness concerns the nature of the injury alleged. It asks whether the alleged injury is something courts recognize to be cognizable for the purpose of Article III standing. See Spokeo, 136 S. Ct. at 1548. Thus, "[f]or example, when an alleged injury is nothing more than 'a bare procedural violation,' there may be no cognizable harm to the plaintiff and thus no concreteness." Hochendoner, 823 F.3d at 731 (quoting Spokeo, 136 S. Ct. at 1549). Here, by contrast, we have actual economic loss, which is the prototypical concrete harm. See Danvers Motor Co. v. Ford Motor Co., 432 F.3d 286, 291 (3d Cir. 2005).

Last, we consider whether the injury is "actual or imminent," as opposed to "conjectural or hypothetical." This requirement "ensures that the harm has either happened or is

sufficiently threatening; it is not enough that the harm might occur at some future time." Katz, 672 F.3d at 71; see also Clapper v. Amnesty Int'l USA, 568 U.S. 398, 409 (2013) (requiring an injury to be "certainly impending"); McInnis-Misenor v. Me. Med. Ctr., 319 F.3d 63, 68 (1st Cir. 2003) (requiring some "immediacy or imminence to the threatened injury"). In this instance, the complaint alleges a harm that has already occurred.

Defendants respond to the foregoing by challenging the assumption on which the claim of actual existing harm is predicated: that a bottle that dispensed smaller drops would not be priced in such a way as to obliterate any cost savings that would result from a consumer's ability to squeeze more drops out of the bottle. The fact that defendants have "discretion to base prices on the number of drops or doses provided," they say, renders plaintiffs' theory of injury speculative.

Assessing the ultimate merits of plaintiffs' "but-for" pricing scenario could indeed keep an economist busy for a while, given the unusual market posited by the complaint in which a large number of companies independently forgo what seems like a profit maximizing opportunity of lowering marginal costs. Be that as it may, plaintiffs expressly allege that scientific studies and the admission of a marketing executive for one of the major defendants all state that consumer cost would fall to some degree were the drops smaller. At this stage of the case, these allegations are

enough to satisfy the minimal plausibility standard applicable to our assessment of the complaint.

Defendants also contend that plaintiffs suffered no injury because they received the "benefit of the bargain." Plaintiffs bought an "effective product, consume[d] it fully," and now, defendants say, "seek a partial refund solely on the basis of their belief that the product should have been more efficiently designed."

This argument sweeps too broadly. Suppose, for example, that defendants successfully conspired directly to fix prices on any competing products, or entered into a similar collusive agreement to, perhaps, sell products with unnecessarily large drops while holding price constant. It would still be true that consumers bought an "effective product, consume[d] it fully" and now "seek a partial refund" solely based on their belief that the price should have been lower. Yet certainly in such a case the aggrieved consumer who directly purchased the product would have standing to sue for the anticompetitive surcharge. Similarly, if the consumers alleged similar conduct but instead brought their cause of action under an applicable price-gouging statute, we would have no trouble concluding that plaintiffs would have standing (as defendants conceded at oral argument). What differs here is the nature of the alleged duty violated by the defendant. But defendants do not explain how that difference bears on the

concreteness of plaintiffs' alleged injury, nor do we see how it would.

Finally, defendants contend that plaintiffs' theory rests on speculation because, in order for a "but for" world to exist in which plaintiffs could benefit from a bottle that dispensed smaller drops, the FDA would have to approve that bottle design and doctors would have to prescribe medications using that design. Pointing to Clapper, 568 U.S. at 414, they argue that plaintiffs' theory rests on "speculation about the decisions of independent actors." Clapper, though, spoke of the speculation inherent in a claim of injury that might arise in the future as the result of decisions by independent actors. Here, the alleged injury (the claimed overpayment) has already occurred, and does not "require guesswork as to how independent decisionmakers will exercise their judgment." Clapper, 568 U.S. at 413. The only relevant uncertainty is whether defendants can show that they lacked the ability to change their behavior that was causing the alleged harm.

We therefore conclude that plaintiffs satisfy the injury in fact requirement of Article III. The two additional factors in our analysis -- causation and redressability -- follow easily. There can be no real dispute that plaintiffs' claim of injury traces itself directly to the challenged conduct. Nor can there be any doubt that plaintiffs' financial injury can be redressed by

damages. Plaintiffs, therefore, have standing to assert their cause of action.

In reaching this conclusion, we do not write on a blank slate. Two other circuits have decided this issue. Our decision is in accord with that of the Third Circuit. See Cottrell v. Alcon Labs., 874 F.3d 154, 159 (3d Cir. 2017). And although the Seventh Circuit has dismissed a similar suit on what appear to be standing grounds, see Eike v. Allergen, 850 F.3d 315, 318 (7th Cir. 2017), we agree with the Third Circuit that the rationale in Eike is more appropriately aimed at the merits. See Cottrell, 874 F.3d at 165-66 (stating that the Seventh Circuit in Eike "blended standing and merits together in a manner that the Supreme Court has exhaustively cautioned against"). Satisfied that we have jurisdiction, we turn to the merits.

III.

Plaintiffs seek a judgment based on an allegation that defendants have breached duties owed to plaintiffs under various state laws. For present purposes, we assume without deciding that plaintiffs correctly describe the duties owed and breached under state law. The question is whether application of those state laws is preempted by federal law. In analyzing this question, "we are not wedded to the lower court's rationale, but may affirm the

order of dismissal on any ground made manifest by the record." Katz, 672 F.3d at 71 (brackets omitted).

The principles of federal preemption that control our disposal of this appeal are not in dispute. If a private party (such as the manufacturers here) 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. See PLIVA, Inc. v. Mensing, 564 U.S. 604, 620 (2011); In re Celexa & Lexapro Mktg. & Sales Practices Litig., 779 F.3d 34, 41 (1st Cir. 2015). Conversely, a private party's ability to do without prior agency approval that which state law requires defeats a preemption defense even if the federal regulatory agency "retains authority to reject [the] changes," unless the defendant establishes by clear evidence that the agency would, in fact, reject the changes. Wyeth v. Levine, 555 U.S. 555, 571-72 (2009). In applying these principles, we proceed de novo, accepting as true all of plaintiffs' well-pleaded facts and drawing all reasonable inferences in plaintiffs' favor. In re Celexa, 779 F.3d at 39.

Defendants point us to an FDA regulation as the source of federal law that purportedly preempts plaintiffs' state law claims. See 21 C.F.R. § 314.70. This regulation governs the manner in which a manufacturer can make a change to an already-approved drug product. It operates by dividing changes into three

categories: major, moderate, and minor changes. The classification of the manufacturer's anticipated alteration into one of these three categories dictates the manufacturer's ability to unilaterally implement its change. Major changes require approval from the FDA prior to implementation, while moderate and minor changes do not. Id. § 314.70(b). Controlling case law is clear -- and plaintiffs here concede -- that if the change they contend state law requires qualifies as "major," then federal law preempts plaintiffs' cause of action because defendants cannot lawfully make such a change without prior FDA approval. See Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 486-87 (2013); PLVIA, Inc., 564 U.S. at 620; In re Celexa, 779 F.3d at 41. Our inquiry thus appears, at first glance, straightforward: Does the change urged by plaintiffs qualify as "major"? If so, our work is done.

But before getting to the meat of this question, we must address a threshold question regarding the interpretation of regulatory text. "Major changes" are defined in section (b) of the FDA regulation. See 21 C.F.R. § 314.70(b). The top level heading -- "(b)" -- is a title: "Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes)." Id. The next level down -- "(b)(1)" -- defines a broad category of qualifying changes:

> A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls,

> equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

Id. (b)(1) (emphasis added). Following, at the same level heading, is section (b)(2), which states: "These changes include, but are not limited to" a host of ensuing categories of changes to drug products, listed at sections (b)(2)(i) through (viii). The threshold question is: To what do the words "[t]hese changes" refer. The answer is relevant because, if "[t]hese changes" refer to the "major changes" in the top level heading "(b)," then all the categories of changes included in section (b)(2) are examples of major changes. Conversely, if the words "[t]hese changes" refer only to the "changes" in section (b)(1), then perhaps any category identified in section (b)(2) must also be shown to have a "substantial potential to have an adverse effect" in order to qualify as "major."[3]

No party or amicus advocates for this latter reading. Nor do we think it the better reading of the text. For one, the

[3] There is also a third possible interpretation: that "[t]hese changes" refer to changes that meet the entire definition provided in (b)(1), i.e., they per se qualify as changes that have a "substantial potential" for an "adverse effect." But since the consequence of this reading -- changes identified in (b)(2) are necessarily major changes -- is the same as the first reading identified above, we do not discuss this possibility in more detail, nor do we rule out the possibility that it might be correct, should it matter in a future case.

inclusion of "[t]hese changes" in a heading of the same level as the broad definition in section (b)(1) (rather than in section (b)(1) itself, or as perhaps in a hypothetical section (b)(1)(i)), makes it unlikely that the "changes" in (b)(2) are a subcategory of the changes in (b)(1). Second, "moderate changes" are defined with the identical broad definition, substituting out only the word "substantial" for "moderate." Thus, if we read "[t]hese changes" in section (b)(2) as referring only to "changes" in section (b)(1), then whether a change is major or moderate would depend in every case on a separate determination of the qualitative magnitude of the change. Third, the categories later defined in section (b)(2) do not map easily onto the types of changes identified in (b)(1). For example, section (b)(2)(v) lists a variety of labeling changes. But in order for this category to have any meaning under the latter reading, labeling changes would have to, in at least some instances, qualify as changes to a "drug substance, drug product, production process, quality controls, equipment, or facilities." Id. § 314.70(b)(1). This, too, makes it more likely that the changes identified in section (b)(2) are a separate category. Finally, neither the Supreme Court nor our court has previously read these regulations to impose a requirement that every major change be shown to have a "substantial potential to have an adverse effect," nor, relatedly, that every moderate change to thus have a "moderate

potential." See Wyeth, 555 U.S. at 568; In re Celexa, 779 F.3d at 37. We therefore conclude that, if a change fits under any of the categories listed in section (b)(2), that change necessarily constitutes a "major" change requiring FDA pre-approval.

With this holding in mind, we turn to the categories of major changes listed in (b)(2). One such category strikes us as particularly applicable:

> Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

21 C.F.R. § 314.70(b)(2)(vi). Under a plain reading, this language establishes three categories of changes that qualify as major. They are: (1) changes in a drug product container closure system that control the drug product delivered to a patient; (2) changes in the type of packaging component that may affect the impurity profile of the drug product; or (3) changes in the composition of a packaging component that may affect the impurity profile of the drug product.

The change urged by plaintiffs to the product dispensing bottle fits comfortably into the first of these categories. The dispensing bottle in which the eye solution is contained is a "drug

product container closure system," the eye solution is a "drug product," and, by dictating the size of the drops, the dispenser "controls" the "drug product delivered" (specifically, its amount) to a patient. Merriam-Webster defines "control" to include "exercise restraining or directing influence over," see Control, Merriam-Webster Collegiate Dictionary (11th ed. 2012), and Black's Law Dictionary defines the word as "to regulate or govern," see Control, Black's Law Dictionary 378 (9th ed. 2009). Dictating the size of the drops dispensed clearly falls within the ambit of these definitions. Indeed, plaintiffs' fundamental complaint is precisely that the FDA-approved current container closure system controls the drug delivered to a patient in a manner that systematically delivers too much medication. If the patient could control the amount of drug product, plaintiffs could simply dispense only the desired 5 to 15 microliter dose, obviating the need to bring this case. It therefore seems quite clear that the change urged by plaintiffs is one to a "drug product container closure system that controls the drug product delivered to a patient," 21 C.F.R. § 314.70(b)(2)(vi), and is for that reason alone a "major" change.

Adding belt to suspenders, regulatory guidance further bolsters our conclusion that a change in the volume of a dispensed drop is a "major" change. In the regulation's preamble, the FDA describes the container closure system category as follows:

> For some drug products, the container closure system itself, rather than a person, regulates the amount of drug product that is administered to a patient. These container closure systems are considered to "control drug delivery." For example, a patient that uses a metered dose inhalation product as instructed cannot control the amount of drug product the container closure system delivers or verify that the appropriate amount has been administered. . . . The design and operation of these container closure systems is critical to ensure that the patient receives the correct dose. A drug product may not be safe or effective if a patient receives too much or too little of the drug product.

Supplements and Other Changes to an Approved Application, 69 Fed. Reg. 18,728, 18,739 (Apr. 8, 2004) (codified at 21 C.F.R. pt. 314). Here, the dispenser determines how much solution -- i.e., "amount of drug product" -- a patient receives. And in a separate document, the FDA lists as "major changes" ones that "may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient . . . ." U.S. Food & Drug Ass'n, Guidance for Industry: Changes to an Approved NDA or ANDA 12 (2004), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf (2004 FDA Industry Guidance). It is hard to conceive that the size of the drops is anything other than a "characteristic[] . . . of the dose delivered."

In the face of the foregoing, plaintiffs offer three retorts.

First, they ask us to rely on a "Highlights" portion of the regulatory preamble to construe section 314.70(b)(2)(vi). As we have just described it, that section expressly classifies as major changes three separate types of changes: "[c]hanges in a drug product container closure system that controls the drug product delivered . . . or changes in the type . . . or composition . . . of a packaging component that may affect the impurity profile." By contrast, the preamble language to which plaintiffs point mentions only two types of changes in describing the section: "FDA has limited the requirement to include only those changes to a drug product container system that involve changes in the type or composition of a packaging component." 69 Fed. Reg. at 18,729. From this language, plaintiffs ask us to conclude that a change that is not to the type or composition of packaging cannot qualify as "major."

We do not share plaintiffs' reading of the preamble. The quoted portion describes not the highlights of the rule, but rather the "Highlights of the Revisions to the Proposed Rule." See 69 Fed. Reg. at 18,729 (April 8, 2004). The category describing as major changes any "[c]hanges in a container closure system that controls drug delivery" was in the proposed rule, see 64 Fed. Reg. 34,606, 34,623 (June 28, 1999), and was not materially changed by these revisions. Hence, it makes sense that a

discussion of the highlights of the revisions includes no mention of the unrevised category.

Later portions of the final rule's preamble confirm this view. When the FDA described this regulatory category outside of the context of discussing revisions to the rule as first proposed, it included within the requirement changes that affect both drug delivery and the impurity profile of the drug product. See 69 Fed. Reg. at 18,739 (describing the relevant provision as regulating container closure systems that "control[] drug delivery or that may affect the impurity profile of the drug" (emphasis added)). In any event, it is well-established that a regulatory preamble is incapable of altering regulatory text's plain meaning. See Christensen v. Harris Cty., 529 U.S. 576, 588 (2000) (holding that an agency's interpretation of its own regulation cannot "overcome the regulation's obvious meaning," as it would "permit the agency, under the guise of interpreting a regulation, to create de facto a new regulation").

We turn next to plaintiffs' second retort. In their reply brief and at oral argument, plaintiffs contend that the provision governing container closure systems is concerned only with devices that "verify" that the "correct dose" has been administered. They claim that "[t]he dose is one drop, no matter its size," and, unlike a metered dose inhaler mentioned in the FDA

guidance, see 69 Fed. Reg. at 18,739, a patient can verify whether "a drop" has been administered.

Neither the text of the regulation nor the substance of the guidance documents define the dose as only the notional unit (e.g., a single drop, no matter how big), rather than the amount of the medication. To the contrary, FDA guidance defines the qualifying changes as ones that "regulate[] the amount of drug product." 69 Fed. Reg. at 18,739 (emphasis added). Because this guidance also defines "drug product" as "[a] finished dosage form, for example, . . . [a] solution[] that contains an active ingredient," a change in the amount of solution dispensed would appear to be a change in the "amount of drug product." 2004 FDA Industry Guidance at 35. And in the very portion of the guidance to which plaintiffs point, the FDA notes that a patient "cannot control the amount of drug product the container delivers or verify that the appropriate amount has been administered." 69 Fed. Reg. at 18,739 (emphasis added). For the reasons already stated, it would appear that a patient using one of defendants' eye solution dispensers cannot "control the amount of the drug product" dispensed. Indeed, as we have already noted, that is precisely the basis of plaintiffs' grievance. Plaintiffs' argument thus fails in its premise.

Finally, plaintiffs allege that drug manufacturers have on five previous occasions changed the drop size of their

prescription eye medication without first obtaining FDA approval. And, in at least one case, they say, the FDA approved of a manufacturer's proposed change even though it had been submitted under the "moderate," rather than "major," changes protocol.[4] As became evident at oral argument, a number of factual questions swirl around plaintiffs' contentions. The parties dispute, for example, whether the manufacturers in these instances did, in fact, make changes sufficiently similar to the one urged here. Nor is it always clear what role the FDA played, if any, in approving the relevant changes. But, given that we are reviewing a dismissal of a complaint for failure to state a claim, we will accept plaintiffs' allegations as true. Even so, they do too little work for plaintiffs.

Deference to an agency's interpretation of its own regulation is "unwarranted when there is reason to suspect that the agency's interpretation 'does not reflect the agency's fair and considered judgment on the matter in question.'" Christopher v. SmithKline Beecham Corp., 567 U.S. 142, 155 (2012) (quoting

[4] Plaintiffs also point to additional documents in which an FDA reviewer appears to have notified a manufacturer that a change in a dropper tip should be submitted through the "moderate" changes protocol, rather than the "minor" changes protocol the manufacturer had originally used. The district court refused to consider these documents, as they had not been mentioned in the complaint, a determination plaintiffs ask us to reverse on appeal. But we need not entertain this contention. For the reasons articulated below, even if we were to consider these additional documents, they are incapable of altering our conclusion.

Auer v. Robbins, 519 U.S. 452, 462 (1997)). Whether sporadic agency action in individual cases is capable of reflecting the "fair and considered judgment" of the agency on a matter of regulatory interpretation is far from clear. This is especially true when the record reflects, as it does here, that the regulatory actions to which plaintiffs point are, in at least some cases, made by mid-level FDA scientists, or even a single "reviewer." And our suspicion of whether such a decision can reflect the "fair and considered" judgment of the agency is even stronger when that decision appears in clear tension with regulatory guidance that almost certainly reflects the agency's considered judgment, and to which courts often defer if it represents a reasonable reading of the text. See, e.g., PLVIA, Inc., 564 U.S. at 613; Rucker v. Lee Holding Co., 471 F.3d 6, 12 (1st Cir. 2006). Additionally, regarding the examples cited by plaintiffs that reflect only FDA inaction, other possible inferences, including the possibility that the FDA used its discretion not to enforce a rule, or that a company otherwise slipped through the cracks, further undermine any probative weight that the examples might hold for plaintiffs' position.

For the foregoing reasons, we therefore conclude that changing the product bottle so as to dispense a different amount of prescription eye solution is a "major change" under 21 C.F.R. § 314.70(b). That conclusion, in turn, means that plaintiffs'

attempt to use state law to require such a change is preempted. See PLVIA, 564 U.S. at 620.

IV.

The decision of the district court is affirmed.