UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

August Term, 2020

(Submitted: April 30, 2021 Decided: August 6, 2021)

Docket No. 20-3643

CARL IGNACUINOS, ON BEHALF OF HIMSELF AND OTHERS SIMILARLY SITUATED, PAMELA DAVIS, ON BEHALF OF HERSELF AND OTHERS SIMILARLY SITUATED,

Plaintiffs-Appellants,

v.

BOEHRINGER INGELHEIM PHARMACEUTICALS INC,

Defendant-Appellee.[*]

Before:

LOHIER and BIANCO, *Circuit Judges*, and ABRAMS, *District Judge*.[**]

The Plaintiffs-Appellants were prescribed a metered-dose inhaler manufactured by the Defendant-Appellee and approved by the Food and Drug Administration (FDA) to alleviate symptoms of chronic obstructive pulmonary disease. The Plaintiffs-Appellants filed this action claiming violations of state law premised on the Defendant-Appellee's allegedly deceptive labeling or

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[*] The Clerk of Court is directed to amend the caption as set forth above.

[**] Judge Ronnie Abrams, of the United States District Court for the Southern District of New York, sitting by designation.

defective design and manufacture of the metered-dose inhaler. Relying largely on the language of the relevant FDA regulation, 21 C.F.R. § 314.70(b), the United States District Court for the District of Connecticut (Underhill, J.) dismissed the claims as preempted by federal law. We **AFFIRM**.

C.K. Lee, Lee Litigation Group, PLLC, New York, NY, *for* Plaintiffs-Appellants Carl Ignacuinos and Pamela Davis.

James T. Shearin, Pullman & Comley, LLC, Bridgeport, CT; Shankar Duraiswamy, Emily S. Ullman, Covington & Burling LLP, Washington, DC, *for* Defendant-Appellee Boehringer Ingelheim Pharmaceuticals, Inc.

LOHIER, *Circuit Judge*:

Plaintiffs-Appellants Carl Ignacuinos and Pamela Davis appeal from a September 25, 2020 judgment of the United States District Court for the District of Connecticut (Underhill, J.), which dismissed their putative class action claims contained in a third amended complaint against Defendant-Appellee Boehringer Ingelheim Pharmaceuticals, Inc. The plaintiffs asserted various state law claims for injuries caused by the alleged deceptive marketing or defective design and manufacture of Boehringer Ingelheim's metered-dose inhaler. The District Court dismissed the complaint in its entirety, holding that the plaintiffs' claims were preempted by federal law. On appeal, the plaintiffs challenge only the dismissal of their design and

manufacturing-related claims. For the reasons set forth below, we **AFFIRM** the judgment of the District Court.

BACKGROUND

For the purpose of resolving this appeal, we accept as true the following allegations in the third amended complaint. See Mirabilio v. Reg'l Sch. Dist. 16, 761 F.3d 212, 213 (2d Cir. 2014).

Boehringer Ingelheim manufactures Combivent Respimat, a metered-dose inhaler that is prescribed to alleviate symptoms of chronic obstructive pulmonary disease (COPD). The Combivent Respimat inhaler, which the Food and Drug Administration (FDA) approved in 2011, consists of an inhaler equipped with a mouthpiece (Respimat) and a cartridge, which contains the medication itself (Combivent). The product's label recommends a dose of "one inhalation four times a day, not to exceed six inhalations in 24 hours," and it represents that the product will deliver 120 metered doses (i.e., 120 "puffs"). App'x 12–13. The inhaler locks and will not spray any more medication after 120 doses have been dispensed. In 2016 the FDA approved an updated version of the labeling of the product, including "Instructions for Use" that noted the possibility that "[t]he dose indicator on the [inhaler]

[may] reach[] zero too soon" under certain circumstances involving user error. App'x 80.

The plaintiffs were prescribed Combivent to alleviate their COPD symptoms. They allege, however, that the Combivent inhalers deliver significantly fewer than the labeled 120 doses, and that they were physically and economically injured as a result. The plaintiffs therefore seek to hold Boehringer Ingelheim liable under Connecticut, Florida, and Indiana state law for alleged design or manufacturing defects that caused the failure to deliver the labeled number of doses.[1]

The District Court dismissed both sets of claims as preempted by federal law. This appeal followed.

DISCUSSION

We review the District Court's dismissal of the plaintiffs' claims de novo. See Dolan v. Connolly, 794 F.3d 290, 293 (2d Cir. 2015). To determine whether the claims are preempted, "we start with the basic principle that under the Supremacy Clause of the Constitution, state and local laws that

[1] The plaintiffs also brought claims premised on Boehringer Ingelheim's alleged misrepresentation of the number of doses on the inhaler's label, but they have abandoned their labeling-related claims on appeal. See Appellants' Br. 7.

conflict with federal law are without effect." UnitedHealthcare of N.Y., Inc. v. Lacewell, 967 F.3d 82, 91 (2d Cir. 2020) (cleaned up); see Gibbons v. Bristol-Myers Squibb Co., 919 F.3d 699, 708 (2d Cir. 2019). The Food, Drug, and Cosmetics Act (FDCA) authorizes the federal Government to regulate the manufacture, labeling, and sale of pharmaceuticals. 21 U.S.C. § 301 et seq.; see Gibbons, 919 F.3d at 707. Design and manufacturing defect claims that a drug manufacturer has breached its duties under state law are preempted by federal law if the manufacturer would require prior FDA approval to comply with those duties. See Gibbons, 919 F.3d at 708. Conversely, the same state claims may proceed if the manufacturer could have acted unilaterally without prior FDA approval. See id.; PLIVA, Inc. v. Mensing, 564 U.S. 604, 620 (2011) (citing Wyeth v. Levine, 555 U.S. 555, 573 (2009)) (explaining that "impossibility" preemption applies when a private party cannot "independently do under federal law what state law requires of it").

When does a drug manufacturer need FDA approval, and when can it act unilaterally without approval? The relevant FDA regulation, 21 C.F.R. § 314.70, makes clear that a manufacturer must obtain prior FDA approval for any "major" changes to the design and manufacturing of already-approved

drug products, but not for "moderate" or "minor" changes. See 21 C.F.R. § 314.70(b)–(d); see also Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 477 (2013) ("Once a drug—whether generic or brand-name—is approved, the manufacturer is prohibited from making any major changes[.]" (citing 21 C.F.R. § 314.70(b)(2))). The question presented on appeal is whether the changes necessary to cure the Combivent inhaler's alleged defects qualify as "major" under § 314.70(b).

We start with "major" changes, which § 314.70(b) defines as follows:

> (b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).
>
> (1) 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.
>
> (2) These changes include, but are not limited to:
>
> (i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved [drug application]; . . .

> (vi) Changes in a drug product container closure system that controls the drug product delivered to a patient . . . ."

21 C.F.R. § 314.70(b). Section 314.70(b)(1) thus tells us how to identify changes that require FDA pre-approval: A change in drug design or manufacturing requires pre-approval if it has a "substantial potential to have an adverse effect." And § 314.70(b)(2) provides a specific but non-exhaustive list of "[t]hese changes."

The provisions that define "moderate" and "minor" changes have a similar structure. They first broadly define a category of changes with "moderate" or "minimal" potential to have an adverse effect. Id. § 314.70(c)(1), (d)(1). They then list specific categories of qualifying changes. Id. § 314.70(c)(2), (d)(2).

On appeal, the plaintiffs argue that a manufacturer must show that a change has a "substantial potential to have an adverse effect" under § 314.70(b)(1) to qualify as "major," even if the change is specifically listed in § 314.70(b)(2). Here, the plaintiffs submit, Boehringer Ingelheim failed to show that the proposed modifications to the inhaler's design or manufacture would have a substantial adverse effect.

We have not previously addressed the argument that a change listed in § 314.70(b)(2) must also separately be proven to have a "substantial potential to have an adverse effect" to qualify as a "major" change. But we agree with the First Circuit in holding 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," regardless of whether the defendant has shown a substantial potential for an adverse effect. Gustavsen v. Alcon Lab'ys, Inc., 903 F.3d 1, 11 (1st Cir. 2018).

As the First Circuit explained, there are three principal reasons for this interpretation and for rejecting the plaintiffs' proposed reading of the regulation. First, section (b)(2)'s non-exhaustive list of qualifying changes is provided "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))." Id. at 10–11. That (b)(2) is not a subpart of (b)(1) "makes it unlikely that the 'changes' in (b)(2) are a subcategory of the changes in (b)(1)." Id. at 11. Second, under the plaintiffs' reading, "whether a change is major or moderate would depend in every case on a separate determination of the qualitative magnitude of the change," which the Supreme Court has never

"previously read these regulations to . . . require[.]" Id. at 11 (citing Wyeth, 555 U.S. at 568); see Bartlett, 570 U.S. at 477. And third, "the categories later defined in section (b)(2) do not map easily onto the types of changes identified in (b)(1)," such that much of the regulatory language in section (b)(2) would not "have any meaning under [the plaintiffs'] reading." Gustavsen, 903 F.3d at 11.

We would add to the First Circuit's compelling analysis only that the authorizing statutory language of 21 U.S.C. § 356a(c)(2) provides that "a major manufacturing change is a manufacturing change that is determined by the [FDA] to have substantial potential to adversely affect the . . . safety or effectiveness of a drug." The FDA's decision to refer to a particular product modification in 21 C.F.R. § 314.70(b)(2)'s list of major changes tells us that it considers the modification's potential to have an adverse effect to be substantial per se. See Supplements and Other Changes to an Approved Application, 69 Fed. Reg. 18,728, 18,736 (Apr. 8, 2004) ("FDA has used this provision of the act [(21 U.S.C. § 356a(c)(2))] to identify a limited number of changes that it considers to have a substantial potential to adversely affect the . . . the safety or effectiveness of a drug.").

For these reasons, we conclude that the plaintiffs' state law design and manufacturing defect claims are preempted to the extent that they would require any change listed in § 314.70(b)(2).

Do the plaintiffs' claims require such a change? Although the complaint broadly alleges that the Combivent inhaler suffered from design and manufacturing defects in violation of various state laws, it proposes no specific changes that might have remedied the defect other than to suggest "a change in the design of the Product so that it actually delivers 120 metered doses," or, "to the extent that the Product's design is sound, but the manufacturing process is compromised, improvements in the manufacturing process." App'x 21–22.[2] Nevertheless, the District Court recognized that an increase in the number of doses delivered would necessarily require either an increase in the amount of Combivent per cartridge or a change in the design of the inhaler to release more doses from the same amount of medication.

With that in mind, we consider whether Boehringer Ingelheim could have unilaterally changed the design of the inhaler to release a different

[2] We assume without deciding that the plaintiffs correctly describe the requirements of state law.

amount of medication per puff. Our answer is no. Section 314.70(b)(2)(vi) provides that any modification to "a drug product container closure system that controls the drug product delivered to a patient" qualifies as a major change. According to the FDA, the paradigmatic product in this category is "a metered dose inhalation product." Supplements and Other Changes to an Approved Application, 69 Fed. Reg. at 18,739 (emphasis added). A patient using a metered-dose inhaler "cannot control the amount of drug product the container closure system delivers or verify that the appropriate amount has been administered." Id. Because the "design and operation of these container closure systems is critical to ensure that the patient receives the correct dose," the FDA "requires information to be submitted to support that the container closure system can accurately and repeatedly deliver the required amount of drug product." Id. So changes to a drug-product-delivering container-closure system such as a metered-dose inhaler are categorically "considered to have a substantial potential to adversely affect . . . the safety or effectiveness of a drug product," and they therefore qualify as major changes. Id.; see also FDA Guidance for Industry: Changes to an Approved NDA or ANDA, 2004 WL 3199016, at *16 (Apr. 1, 2004) (stating that any change to "the

valve or actuator of a metered-dose inhaler" constitutes a "[m]ajor [c]hange[ ]"); Gustavsen, 903 F.3d at 11–12 (changing a prescription eye solution's dispensing bottle to adjust "the size of the drops dispensed" is a "major" change under § 314.70(b)(2)(vi)). Any state law claim premised on a duty to make such a change to the design of the Combivent inhaler is therefore preempted by federal law.

Nor could Boehringer Ingelheim have unilaterally increased the amount of liquid Combivent medication in each cartridge (that is, a change in the product's "fill volume" or "fill weight"). Section 314.70(b)(2)(i)'s list of "major changes" includes "changes in the qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved [drug application]," unless those changes are otherwise "described" in the paragraphs defining "moderate" and "minor" changes. 21 C.F.R. § 314.70(b)(2)(i). The statute from which the regulation derives itself says that any change "made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved [drug] application" qualifies as a major change "unless exempted by the Secretary [of Health and Human Services] by regulation or guidance

from the requirements of this subsection." 21 U.S.C. § 356a(c)(2)(A); see also Supplements and Other Changes to an Approved Application, 69 Fed. Reg. at 18,737 (explaining that the "[e]xemptions by regulation are provided in § 314.70(c) or (d)"). A change in specification or quantitative formulation thus qualifies as a major change unless otherwise provided by the FDA.

The plaintiffs do not dispute that increasing the amount of medication in each Combivent cartridge would change either its "quantitative formulation" or its "specifications." But they argue that increasing the cartridge's fill volume must be a "moderate" or "minor" change because it would not have a substantial potential to have an adverse effect on the safety and effectiveness of the drug product. For the reasons explained above, their argument rests on a misreading of § 314.70(b). We need not independently consider the potential adverse effect of increasing the volume of liquid medication in each cartridge. But even if we did consider it, the FDA's guidance for industry explains that "[a] change in the fill volume of a drug product" involves a change under § 314.70(b)(2)(i) for which "[t]here is no exemption." FDA Guidance for Industry: Changes to an Approved NDA or

ANDA Questions and Answers, 2001 WL 34768253, at *7 (Jan. 1, 2001).[3] Although the FDA's guidance is not binding on this Court, it fully comports with the plain meaning of the regulation, and we find it persuasive. See 21 C.F.R. § 10.115(d)(1) ("[FDA] [g]uidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA."). The plaintiffs, furthermore, have not made us aware of another regulation or guidance that would exempt from the requirement of FDA pre-approval the change in fill volume that they propose here. Their proposed change in fill volume therefore "must be submitted in a prior approval supplement." FDA Guidance for Industry: Changes to an Approved NDA or ANDA Questions and Answers, 2001 WL 34768253, at *7; see 21 C.F.R. § 314.70(b) (defining "major changes" as those "requiring supplement submission and approval prior to distribution of the product").

[3] The FDA Guidance more specifically states that a change in fill volume is a change in "specification." FDA Guidance for Industry: Changes to an Approved NDA or ANDA Questions and Answers, 2001 WL 34768253, at *7. FDA regulations elsewhere define "[s]pecification" to mean "the quality standard . . . provided in an approved [new drug application] to confirm the quality of" a drug product. 21 C.F.R. § 314.3(b). Consistent with the FDA's guidance, we agree that a change in fill volume meets the criteria of § 314.70(b)(2)(i), regardless of whether it does so as a "specification" or a "quantitative formulation" of the drug product.

Setting aside for a moment that the plaintiffs themselves have failed on appeal to point us to any specific regulation that would render an increase in fill volume a "moderate" or "minor" change, we note that the District Court considered whether a particular regulation, § 314.70(c)(6)(ii), applied. We agree with the District Court that that provision does not. Indeed, it helps illustrate why the desired change here is "major." Section 314.70(c)(6)(ii) provides that "[a] change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product" qualifies as a "moderate" change. "The phrase 'labeled amount of [drug] product' refers to the total quantity of drug product (e.g., milliliters, grams)." Supplements and Other Changes to an Approved Application, 69 Fed. Reg. at 18,745. Because a change in the quantity of Combivent per cartridge represents a change in the labeled amount of drug product, it cannot qualify as a moderate change under § 314.70(c)(6)(ii).

There is yet another reason such a change does not qualify as anything less than major. Combivent is a sterile liquid drug product, and the FDA specifically declined to include changes to sterile drug products in

§ 314.70(c)(6)(ii)'s exemption from prior approval. See Supplements and Other Changes to an Approved Application, 69 Fed. Reg. at 18,745. The risk associated with a change in the size or shape of a sterile drug container, the agency explained, is categorically "higher than for nonsterile products." Id. Because even a "minimal" modification "may affect the sterility assurance" of a sterile drug product, such a modification constitutes a "major change." Id. By contrast, "changes in the labeled amount of a nonsterile drug product in a unit-of-use container" have only "moderate potential to adversely affect the safety and efficacy of the drug product," and are appropriately classified as "moderate change[s]" under § 314.70(c). Id. at 18,746 (emphasis added).

Because the modifications that the plaintiffs' claims would require under state law constitute "major" changes, we conclude that those claims are preempted by federal law. The complaint failed to plausibly state any non-preempted claim and was properly dismissed.

CONCLUSION

We have considered the plaintiffs' remaining arguments and conclude that they are without merit. For the foregoing reasons, the judgment of the District Court is **AFFIRMED**.