In the

United States Court of Appeals

For the Seventh Circuit

No. 17-2056

RODNEY GUILBEAU, et al.,

Plaintiffs-Appellants,

v.

PFIZER INC. and PHARMACIA & UPJOHN COMPANY LLC,

Defendants-Appellees.

Appeal from the United States District Court for the
Northern District of Illinois, Eastern Division. MDL No. 2545
Master Docket Case No. 1:14-cv-1748 — **Matthew F. Kennelly**, *Judge.*

ARGUED OCTOBER 23, 2017 — DECIDED JANUARY 19, 2018

Before BAUER and HAMILTON, *Circuit Judges*, and DARROW, *District Judge.*[*]

HAMILTON, *Circuit Judge*. In *Wyeth v. Levine*, the Supreme Court held that claims against a manufacturer of a brand-name prescription drug for failure to warn adequately of the drug's dangers were not preempted by federal law. 555 U.S.

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[*] Of the Central District of Illinois, sitting by designation.

555, 581 (2009). In *PLIVA, Inc. v. Mensing*, the Supreme Court held that such failure-to-warn claims against manufacturers of generic drugs are preempted by federal law. The different results, the Court explained in *Mensing*, are based on the different regulatory requirements and processes for approving and labeling prescription drugs. 564 U.S. 604, 614, 618, 625 (2011).

This appeal arises from the district court presiding over thousands of related claims against manufacturers of testosterone replacement therapy drugs. We must consider how to apply *Levine* and *Mensing* to a manufacturer of a drug that does not fit neatly into the colloquial dichotomy between brand-name and generic drugs. We must look at the more precise legal and regulatory context underlying those terms, focusing on whether the U.S. Food and Drug Administration (FDA) approved public sale of the drugs through the "new drug application" or NDA process, or instead through the "abbreviated new drug application" or ANDA process. We have tried to minimize use of impenetrable acronyms, but readers are warned that some are unavoidable.

Testosterone replacement drugs have been sold for more than sixty years as prescription drugs with the approval of the FDA. The drugs have long been used to treat low testosterone production in younger men. In recent years, though, manufacturers have found a new market for these drugs to counteract the effects of declining testosterone production in older men. Older men experience a higher incidence of heart attacks, strokes, and other cardiovascular events than younger ones. Numerous lawsuits have been filed against testosterone drug manufacturers alleging that the drugs increase these

health risks. One theory in such cases is that the drug manufacturers have failed to warn doctors and patients adequately about the risks, a tort theory arising under state product-liability laws. Such cases pending in federal district courts have been consolidated for discovery and pretrial proceedings in a multi-district litigation (MDL) docket before Judge Kennelly in the Northern District of Illinois. See 28 U.S.C. § 1407.

The district court granted a motion to dismiss brought by the manufacturers of one testosterone replacement drug, Depo-T, on the ground that failure-to-warn claims are preempted by federal law. The district court found that Depo-T's manufacturers could not change their drug labels to add additional warnings because FDA regulations prohibit them from "making a unilateral labeling change." *In re Testosterone Replacement Therapy Products Liability Litig.*, 142 F. Supp. 3d 747, 754, 755 (N.D. Ill. 2015). Plaintiffs appeal that decision, as well as the district court's related decision to deny further discovery related to the preemption defense. We affirm both decisions.

Part I explains the regulatory approval process for prescription drugs and the particular historical context and procedural background needed to understand the issues in this appeal. Part II analyzes the defendant drug-makers' preemption defense. Part III reviews the district court's decision to deny further discovery on the preemption defense.[1]

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[1] This single appeal covers more than one thousand individual cases before the MDL transferee court. On appeal, it has become clear that complete diversity of citizenship is lacking in forty of the cases covered by this appeal. See App. Dkt. 15-1, at 5–7. By separate order today, we vacate the dismissals on the merits in those forty cases despite our affirmance in all the other cases where federal subject matter jurisdiction is secure. Those

I. *Factual Background and Procedural History*

A. *Regulatory Background*

Prescription drugs in the United States must be approved by the Food and Drug Administration (FDA) before they can be sold. 21 U.S.C. § 355(a). Prospective drugs can follow one of two general paths to obtain FDA approval. A new drug that has never been marketed before must be approved through the new drug application (NDA) process. The NDA process requires an extensive series of safety and effectiveness trials before a new drug can be sold. See § 355(b)(1).

If the prospective drug is "the same as" an existing drug already on the market, however, the maker can obtain approval through the shorter and less onerous abbreviated new drug application (ANDA) process. See § 355(j)(2)(A). The ANDA process requires proof that the drug in question has the same active ingredients, effects, and labeling as a predecessor drug that the FDA has already approved. *Id.*; 21 C.F.R. § 314.94(a) (2015). The predecessor drug that has already received FDA approval is known as the reference listed drug (RLD). 21 C.F.R. § 314.3(b). In many cases, the reference listed drug is the original drug that pioneered a new active ingredient or a new treatment and gained FDA approval through the new drug application process. If the original pioneer drug has been discontinued, the FDA will typically designate the remaining market-leading drug to take its place as the reference listed drug for that particular category of drugs. See below at 17.

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forty cases must be remanded to the district court to resolve the jurisdictional problems.

NDA-approved drugs are often referred to as "brand-name" drugs and ANDA-approved drugs as "generic" drugs. These colloquial terms are not quite precise enough for our purposes in this case, though. The 1984 Hatch-Waxman Act established the current drug approval processes and the associated patent protection for truly new drugs. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. 98-417, 98 Stat. 1585; H.R. Rep. No. 98-857, at 14–15 (1984); *Mensing*, 564 U.S. at 612 & n.2.[2] Depo-T, the drug at issue in this appeal, has a trademarked name and was approved long before the 1984 changes, but the FDA has classified Depo-T as an ANDA-approved drug (i.e., a "generic") under current law. See Supp. App. at 41, 55.

The approval process is central to both the preemption issue here and the difference between the Supreme Court's preemption decisions in *Levine* and *Mensing*. Those decisions turn on whether a drug-maker may or may not change its label to add a warning without prior approval from the FDA. *Levine* held that if the drug-maker may make such unilateral changes, then federal law does not preempt a state-law claim based on an inadequate label. Federal law thus would not prevent the drug-maker from complying with a state statute or court decision requiring more cautious warnings than appear

[2] For further background on the drug approval process, see FDA, Center for Drug Evaluation and Research, Determining Whether To Submit an ANDA or a 505(b)(2) Application: Guidance for Industry (Draft Guidance) 1–5 (Oct. 2017); Suzanne M. Kirchhoff et al., Congressional Research Service, Frequently Asked Questions About Prescription Drug Pricing and Policy 2 & n.b (May 2017) (explaining "Generic Drug" and Hatch-Waxman).

on the FDA-approved label. 555 U.S. at 573 (rejecting preemption defense for NDA-holder).

The issue is governed by an FDA regulation known as the "changes-being-effected" (CBE) regulation, which permits "changes in the labeling to reflect newly acquired information" in advance of later FDA approval. 21 C.F.R. § 314.70(c)(6)(iii). The regulation allows a unilateral change "to add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association" meets FDA standards. § 314.70(c)(6)(iii)(A). The Supreme Court has interpreted the CBE regulation to be available only if the drug in question was approved through the NDA process, but not if it was approved via the ANDA process because ANDA-approved "generic" drugs may change their labels only with the FDA's approval or at the FDA's request. See *Mensing*, 564 U.S. at 614–15, 623–26 ("We … conclude that the CBE process was not open to the [ANDA holder] Manufacturers for the sort of change required by state law.").[3] The *Mensing* Court held that this difference in approval procedures is decisive for preemption:

> We recognize that from the perspective of [plaintiffs] Mensing and Demahy, finding pre-emption here but not in *Wyeth* [*v. Levine*] makes little sense. Had Mensing

[3] Perhaps for the sake of readability, the *Mensing* Court referred to drugs approved pursuant to new drug applications (NDAs) as "brand-name" drugs and those approved pursuant to abbreviated new drug applications (ANDAs) as "generic" drugs. When one reads *Mensing* together with the cited regulations, see 564 U.S. at 612 n.2, 616–17, and the cited passages from the FDA's amicus brief in that case, see 564 U.S. at 614, it is clear that *Mensing* used the terms brand-name and generic interchangeably with the FDA terms NDA-approved and ANDA-approved.

> and Demahy taken Reglan, the brand-name drug prescribed by their doctors, *Wyeth* would control and their lawsuits would not be pre-empted. But because pharmacists, acting in full accord with state law, substituted generic metoclopramide instead, federal law pre-empts these lawsuits.

Id. at 625. The *Mensing* decision did not address the concept of reference listed drugs (RLDs) in any meaningful detail. See *id.* at 612, 614. With this background, we turn to the specific drugs in this appeal.[4]

B. *FDA Approval of Depo-Testosterone*

In 1953, the Food and Drug Administration approved a new drug, Delatestryl, as a testosterone replacement injection. Its original purpose, according to the new drug application filed on its behalf, was to treat men whose bodies did not produce enough testosterone naturally. This NDA came before many of today's regulatory requirements, though Delatestryl later passed effectiveness screening in the 1960s as required under the then-new Drug Efficacy Study Implementation program.

In 1979, the FDA approved the Upjohn Company's abbreviated new drug application (ANDA) for Depo-Testosterone, a testosterone injection similar to Delatestryl. Depo-T, as the

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[4] As in *Mensing*, we are concerned in this appeal only with the CBE regulation's availability to "add or strengthen a … warning" without prior FDA action. 21 C.F.R. § 314.70(c)(6)(iii)(A). The CBE regulation might be available to ANDA holders for other purposes not addressed in *Mensing* and thus not relevant to this appeal. See, e.g., FDA, *Generic Drug Labeling Revisions Covered under Section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act*, Manual of Policies and Procedures § 5230.3 (2013).

product is still called, produced safety and effectiveness results equivalent to those of Delatestryl. Under the drug approval process at the time, similar results sufficed for streamlined ANDA approval. But because of a slight difference in its physical composition that made it not quite the same as Delatestryl, after the 1984 statutory changes were implemented, Depo-T became the reference listed drug (RLD) for its precise kind of testosterone injection. This meant that any drugs seeking to follow in Depo-T's footsteps had to demonstrate bioequivalence to (i.e., that they were the same as) Depo-T to qualify for the streamlined approval process of an abbreviated new drug application. See above at 4; see also 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.3(b). When these lawsuits were filed, defendant Pfizer had taken over production and marketing of Depo-T, and the drug remained the reference listed drug. More than half a dozen other testosterone drugs have followed Depo-T's lead since its approval in 1979.

C. *Procedural History*

Testosterone replacement drugs like Depo-T gained new life in recent years as doctors began prescribing them to aging men with health conditions possibly related to low testosterone levels (known in some marketing campaigns as "Low T"). By 2014, however, a sizable number of men treated with testosterone replacement drugs had filed suits against drugmakers alleging that the drugs caused heart attacks, strokes, and other cardiovascular problems. In June 2014, such cases pending in federal courts were transferred to the Northern District of Illinois for consolidated discovery and pretrial proceedings under the title *In re: Testosterone Replacement Therapy Products Liability Litigation* (MDL 2545). See 28 U.S.C. § 1407.

The broader MDL against the makers of testosterone replacement products continues, involving numerous products and defendants and thousands of plaintiffs.

This appeal is limited to just one issue about one drug: whether failure-to-warn claims under state law against Depo-T's maker are preempted by federal law. The plaintiffs allege that the testosterone replacement drug-makers violated state product-liability law when they failed to warn the plaintiffs and their doctors adequately about the potential side effects of the drugs. These warnings, the plaintiffs allege, should have appeared in the drug's labeling.

The district court decided that federal law preempted state failure-to-warn claims for all drugs approved pursuant to an abbreviated new drug application. The court granted a motion to dismiss all such claims, which covered claims against Depo-T. 142 F. Supp. 3d 747, 754 (N.D. Ill. 2015). The court rejected plaintiffs' effort to avoid preemption by emphasizing that Depo-T was also the reference listed drug: "RLD ANDA holders are prohibited under federal law from unilaterally changing their drugs' warning labels" just like any other ANDA holder. *Id.* The district court also denied further discovery into two instances from the 1990s where it seemed that Depo-T's label was changed through the changes-being-effected process for other reasons. *Id.* at 754–55. The district court denied reconsideration. No. 14 C 1748, 2016 WL 861213 at *2 (N.D. Ill. Mar. 7, 2016). Plaintiffs have appealed both rulings.

II. *Preemption*

A. *Generic Drug Labeling and Preemption at the Supreme Court*

The district court granted a Rule 12(b)(6) motion to dismiss on preemption grounds, a legal determination that we review *de novo*. *Toney v. L'Oreal USA, Inc.*, 406 F.3d 905, 907–08 (7th Cir. 2005). Preemption comes in several forms, but in these disputes over drug labels, conflict preemption takes center stage. E.g., *Mason v. Smithkline Beecham Corp.*, 596 F.3d 387, 390 (7th Cir. 2010). State-law tort claims alleging that a drug label failed to warn consumers adequately of potential dangers may be preempted because of the extensive labeling requirements imposed by federal law. See *id.* at 391–96. In essence, tort litigation can place a state-law duty on drug-makers to warn adequately of the material risks involved in using their products. The FDA also imposes labeling duties under federal law in the drug approval process. When these state and federal duties create "an actual conflict between state and federal law such that it is impossible for a person to obey both," federal law controls and the state-law tort claims must be dismissed. See *id.* at 390.

As summarized above, a series of recent Supreme Court decisions on federal preemption in failure-to-warn cases involving prescription drugs has narrowed our task. In *Wyeth v. Levine*, 555 U.S. 555, 568 (2009), the Supreme Court zeroed in on whether the changes-being-effected regulation could allow a brand-name drug manufacturer to comply with both federal law and state law requiring warnings that went beyond those on the FDA-approved label. The Court found that the changes-being-effected regulation, 21 C.F.R. § 314.70(c),

permits label changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction," and—critical to the preemption issue—changes by eligible application holders "need not wait for FDA approval." *Levine*, 555 U.S. at 568. The *Levine* Court concluded that the changes-being-effected regulation was available for "brand-name" drugs approved through NDAs, which covered the drug at issue there. Because the changes-being-effected regulation "permitted Wyeth to unilaterally strengthen its warning" and Wyeth could not demonstrate that the FDA would have "prohibited such a change," the Vermont jury award stood. *Id.* at 573. Wyeth, in short, had "failed to demonstrate that it was impossible for it to comply with both federal and state requirements" because the changes-being-effected regulation was available to add new warnings without delay. *Id.*

In *PLIVA, Inc. v. Mensing*, the Supreme Court narrowed the holding of *Levine*, limiting it to brand-name drugs approved through NDAs. 564 U.S. 604 (2011). The issue in *Mensing* was "whether, and to what extent, *generic* [drug] manufacturers may change their labels after initial FDA approval" of an ANDA. *Id.* at 613 (emphasis altered). The FDA explained in an amicus brief that it had "consistently taken the position that an ANDA holder"—i.e., a generic drug-maker—"may not unilaterally change its approved labeling" using the changes-being-effected regulation. Brief for the United States as Amicus Curiae Supporting Respondents at 16, *Mensing*, 564 U.S. 604 (No. 09-993), 2011 WL 741927, at *16. The *Mensing* Court accepted this reading of the changes-being-effected regulation, extending deference to the agency's interpretation of its own regulations. 564 U.S. at 614–15. Given its approving citation, see *id.* at 616–17, the Court seemed particularly con-

vinced by the 1992 explanation the FDA offered in its preamble to the ANDA regulations. There the agency explained that only the FDA—and not the ANDA holder—had the power to decide whether new warnings were needed:

> After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992). Accordingly, the preemption defense was available to the ANDA holders in *Mensing* even though it had not been available to the NDA holder in *Levine*.

Warnings could not have been added without FDA approval in *Mensing* because ANDA holders "have an ongoing federal duty of 'sameness.'" 564 U.S. at 613. At all times their drugs' labeling "must be the same as the listed drug product's labeling" that was the basis of the ANDA approval. *Id.*, quoting 57 Fed. Reg. at 17,961. Since the only thing left for ANDA holders to do in that case was to petition the FDA to approve a labeling change, the drug-makers could not "independently satisfy [their] state duties for pre-emption purposes," and the state-law tort claims were preempted. *Id.* at 624; see also *Mutual Pharm. Co. v. Bartlett*, 570 U.S. —, —, 133 S. Ct. 2466, 2480 (2013) (*Mensing*'s holding—that the availability of the changes-being-effected regulation determines preemption—turns what could otherwise be a complex impossibility analysis into a "straightforward application of pre-emption law").

B. *The MDL Plaintiffs' Preemption Arguments*

Plaintiffs here seek to avoid the preemption holding of *Mensing* by pointing to a small but, they say, critical, factual difference. Yes, Depo-T was approved through an ANDA, like the generic drug in *Mensing*, but plaintiffs point out that Depo-T is also the reference listed drug (RLD) for its family of testosterone replacement drugs. Because the federal duty of sameness attaches to the RLD's labeling (which is not always a drug approved via an NDA), and because Depo-T itself is the RLD, plaintiffs believe that "Pfizer's obligation is to maintain a label identical to the RLD – that is, identical to itself." Appellants' Br. at 27. "Because the only label with which Pfizer must maintain identity is the label for Depo-T itself," plaintiffs reason, "nothing in the FDA regulations precludes Pfizer from using the CBE procedure to add warnings to the Depo-T label." *Id.* Any unilateral changes would not lead to inconsistent labeling because Depo-T's label would always match its own and thus comply with federal law, or so this theory goes.

Even if the RLD v. not-RLD distinction alone is insufficient to avoid preemption, plaintiffs argue further, Depo-T's age and unusual timeline of approval should distinguish it from the situation in *Mensing*. Depo-T is an RLD made by an ANDA holder "for which there never was an NDA-holder." *Id.* As noted, Depo-T's ANDA was approved in 1979 before Congress established the current approval regime. Because of this idiosyncrasy, plaintiffs suggest, none of the FDA interpretations the Court found important in *Mensing* should bar Pfizer from using the changes-being-effected regulation to add new warnings required by state law, so preemption should not apply to bar plaintiffs' claims.

C. *Availability of the Changes-Being-Effected Regulation*

1. *Summary*

We disagree with the plaintiffs' efforts to avoid applying *Mensing* to Depo-T. We reach this conclusion for two principal reasons. First, we read *Mensing* to bar any use of the changes-being-effected regulation to strengthen warnings by any ANDA holder, whether it is the reference listed drug or not. This is an interpretation drawn from the drug approval statutes and regulations that apply to all ANDA drugs. Second, we conclude that RLD ANDA holders are not under a different duty of sameness. Like all other ANDA holders, they must match the labeling for the RLD *already approved* by the FDA, which in their case refers to their own prior approved labeling. These reasons accord with a decision of the Sixth Circuit on this issue and show why the plaintiffs' claims are preempted by federal law despite Depo-T's unusual history.

2. *CBE Changes Are Not Available to ANDA Holders to Add Warnings*

Mensing instructs that no ANDA holder may use the CBE regulation to add or strengthen a warning on its own. *Mensing*, 564 U.S. at 614 ("CBE changes unilaterally made to strengthen a generic drug's warning label would violate the [relevant] statutes and regulations"); see also above at 6–7. That conclusion, drawn from the applicable drug labeling statutes, regulations, and FDA interpretations, applies with equal force to ANDA holders whose drugs are also RLDs.

First, despite potentially confusing references to brand-name and generic drugs—recall that the relevant FDA terms are NDA-approved and ANDA-approved, respectively—

Mensing itself unambiguously refers to the lines drawn in the drug approval process as determining access to the CBE regulation. *Mensing* concludes that while NDA holders may use the CBE regulation to add warnings, ANDA holders (like Pfizer here) may not. Responding to the criticism that finding pre-emption in *Mensing* but not in *Levine* made little sense, the *Mensing* Court observed that "the federal statutes and regulations that apply to brand-name drug manufacturers are meaningfully different than those that apply to generic drug manufacturers," *id.* at 626.

Despite their occasional use of these terms, the Supreme Court, Congress, and the FDA all agree that the meaningful difference is found in approval process classifications, not shorthand terms like brand-name and generic. Like the *Mensing* Court, see 564 U.S. at 612 n.2, the FDA treats "brand-name drug" as a synonym for a "drug approved in an NDA" and "generic drug" as a term referring to the product of an ANDA holder. See Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,985, 67,988, 67,998 (proposed Nov. 13, 2013) (to be codified at 21 C.F.R. § 314.70). The distinction between NDAs and ANDAs comes directly from statute. Compare 21 U.S.C. § 355(b)–(c) with 21 U.S.C. § 355(j). In addition, the classifications set forth in 21 C.F.R. § 314.50 et seq. (NDAs) and 21 C.F.R. § 314.92 et seq. (ANDAs) do not distinguish drugs on the basis of whether they are used as RLDs for later applications.[5] As Depo-T itself demonstrates, having a registered

[5] The parties dispute the significance of a recent change to these regulations. See Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69,580 (Oct. 6, 2016). *Mensing* is based on the fact that NDA holders and ANDA holders are subject to different rules. 564 U.S. at

trademark name and being designated as an RLD does not change a drug's approval process classification at FDA. See Supp. App. at 41, 52.

One of the statutes cited in *Mensing* emphasizes another key detail about what it means to be an RLD under the ANDA approval process. Until the FDA acts, what matters to ANDA holders in this context is not which drug is currently the RLD, but rather which drug *was* the RLD when the ANDA was submitted. For initial approval, a maker of an ANDA-approved drug must show that its labeling will be "the same as the labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(A)(v); see also *Mensing*, 564 U.S. at 612–13 (citing this language). *Mensing* clarifies that this is a continuing duty: ANDA drug labeling "must always be the same" as labeling for the "listed drug product" designated by the FDA. *Id.* at 613, quoting Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992); see also *Mensing*, 564 U.S. at 618 (defining an ANDA holder's "federal law duty to keep the label the same"). Unless and until the FDA decides the labeling needs to change, ANDA holders must

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625. One such rule is that NDA holders may use the CBE regulation to add warnings unilaterally, without prior FDA approval, while ANDA holders may not. This basic point is not affected by the recent rule update, which was described as a set of "technical amendments … intended to promote clarity and consistency." 81 Fed. Reg. at 69,630. The specific update at issue here was presented under the heading "Consistent Use of Defined Terms." See *id.* Nowhere in that 2016 rule change does FDA indicate that it is departing from its 2013 position that ANDA holders may make CBE labeling changes only "to conform with *approved* labeling for the RLD." 78 Fed. Reg. at 67,988 (emphasis added); see also below at 18–19. If the 2016 rule change had been meant to alter this earlier understanding, it would have said as much.

match the FDA-approved language for the RLD, not whatever the RLD's manufacturer currently thinks would be best. See below at 20–23.

The ANDA regulations cited in *Mensing* further reinforce this conclusion that approval-process status and RLD status are separate. See 564 U.S. at 613, citing ANDA Regulations, 57 Fed. Reg. at 17,961. For example, when the sale of an RLD is discontinued, to remain current the FDA must select a new RLD for that type of drug from among those still on the market. If no NDA-approved drug is left in circulation, the replacement RLD is selected on the basis of its market share. This new RLD will remain designated as such even if its market share later shrinks.[6] What actually matters in terms of choosing an RLD, then, is simply that the FDA needs a new RLD and the selected drug continues to be sold in the market. Plaintiffs have not directed us to an authoritative FDA interpretation that says taking on RLD status also confers new la-

[6] In implementing the current NDA and ANDA approval regime, the FDA explained:

> As stated above, FDA has revised the rule so that FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be *the market leader as determined by FDA on the basis of commercial data*. … Once FDA designates that reference listed drug, that drug will continue to be the reference standard even if the drug is later replaced as the market leader.

ANDA Regulations, 57 Fed. Reg. at 17,958 (emphasis added).

beling abilities and responsibilities on that drug's manufacturer. See Appellants' Br. at 27–33. By itself, the RLD designation does not change the preemption analysis under *Mensing*.

For purposes of the changes-being-effected regulation, the key distinction to both the Supreme Court and the FDA is the approval process, not RLD status. The statutes, the regulations, and the *Mensing* opinion do not draw the distinction plaintiffs advocate: a difference in abilities and responsibilities between RLD ANDA holders and other ANDA holders.

Second, the FDA has already interpreted *Mensing* as prohibiting any ANDA holder, whether it is the RLD or not, from using the changes-being-effected regulation to add a warning without prior FDA approval. In November 2013, after *Mensing* was decided, the agency proposed a rule change that for the first time would "expressly provide that ANDA holders may distribute revised labeling that differs from the RLD upon submission of a [changes-being-effected] supplement to FDA." Labeling Changes for Approved Drugs, 78 Fed. Reg. at 67,989.[7] If adopted, this change "would create parity between NDA holders and ANDA holders" with respect to adding warnings using the CBE regulation. *Id.* This action, if finalized, "may eliminate the preemption of certain failure-to-warn claims with respect to generic drugs," *id.* at 67,989—a prediction the FDA offered immediately after the agency discussed the *Levine* and *Mensing* decisions in detail. *Id.* at 67,988–89.

[7] This proposed rule change has not received final approval. Compare 78 Fed. Reg. at 67,998 (proposing new paragraph (8) to be titled: "Equal applicability to application holders and abbreviated application holders") with 21 C.F.R. § 314.70(c) (2017) (ending at paragraph (7)).

The FDA's discussion of the issue did not signal any difference in abilities or responsibilities between RLD and non-RLD ANDA holders. In fact, this proposed change would further make clear that "the duty to maintain accurate product labeling does not differ between an ANDA designated as the reference standard for bioequivalence studies and other approved ANDAs." *Id.* at 67,989.[8] The FDA explained that unless this rule change took effect, under *Levine* and *Mensing*, "access to the courts is dependent on whether an individual is dispensed a brand name or generic drug," *id.* at 67,988, with no reference to whether that dispensed drug was an RLD or not.

This proposed rule change from 2013 thus indicates several things. The FDA believes its current rules apply equally to all ANDAs, whether they are RLDs or not. The FDA considered making a uniform preemption policy change that would apply equally to all ANDA holders. And the FDA thought this change "would create parity between NDA holders and ANDA holders," indicating that these CBE changes would have effect only prospectively and not retroactively. *Id.* at 67,989. For now this remains only a proposed rule change, but it sheds light on the FDA's understanding of current law.

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[8] There is a slight difference between the terms "reference listed drug" and "reference standard," see 21 C.F.R. § 314.3(b), but the FDA gives no indication that this distinction is material to preemption or that it matters for the purposes of the proposed rule. See Labeling Changes for Approved Drugs, 78 Fed. Reg. at 67,989; see also FDA, Center for Drug Evaluation and Research, Draft Guidance: Referencing Approved Drug Products in ANDA Submissions 6 (January 2017); 21 C.F.R. § 314.94(a)(3). Instead, this illustration indicates that all ANDAs are treated alike for purposes of preemption, in the eyes of the FDA.

Plaintiffs are asking us in effect to recognize a third category in a highly regulated context where the relevant agency and the Supreme Court have recognized only two. Rather than basing preemption on the difference between an NDA and an ANDA, as *Levine* and *Mensing* do, plaintiffs contend we should put labeling claims against NDA holders and RLD ANDA holders on one side (not preempted) and those against all other ANDA holders on the other (preempted). This change would enable a new category of plaintiffs to pursue labeling claims against a subset of drug-makers in situations that we recognize may involve "dreadful injuries" and "passionate responses." *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. —, —, 133 S. Ct. 2466, 2478 (2013). We do not see, however, a statutory or regulatory basis for drawing the line that plaintiffs propose.

3. *All ANDA Holders Share an Identical Duty of Sameness*

The second principal reason plaintiffs' claims are preempted is that ANDA drugs that are also RLDs have a duty of sameness indistinguishable from that of all other ANDA drugs. As mentioned in *Mensing*, by statute, all ANDAs must show that "the labeling proposed for the new drug is the same as the labeling *approved* for the listed drug" in a side-by-side comparison. 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added); see also *Mensing*, 564 U.S. at 612–13 (citing statute and establishing that this is a continuing duty of ANDA holders).

The statute uses the past tense ("approved") to describe the labeling that ANDA holders must match. This language signals that all ANDAs must mirror the version of the RLD's labeling that was previously approved by the FDA. See FDA, Center for Drug Evaluation and Research, Guidance for Industry: Revising ANDA Labeling Following Revision of the

RLD Labeling 4 (2000) (explaining that "approved changes in the RLD labeling generally necessitate changes in the labeling of … ANDAs using the RLD"). Put another way, the duty of sameness does not attach to whatever labeling the RLD is currently using but rather to the labeling the FDA has already approved for the drug, whether the approval happened recently or long ago. Pfizer may not unilaterally change the FDA-approved language on Depo-T's label. A lawsuit under state law that seeks to recover damages for Pfizer's failure to do so is preempted by federal law.[9]

Two examples help illustrate why this is the case. Consider first what would happen if the label for a brand-name (NDA) drug that is also an RLD were changed through the CBE pro-

[9] The duty of sameness applies throughout the life of the ANDA-approved drug since the definition of an ANDA includes "all amendments and supplements to the application." 21 C.F.R. § 314.3(b). Plaintiffs contend that another regulation relieves the apparent statutory burden of matching the FDA-*approved* version of the RLD's label. FDA may withdraw an ANDA's approval after the drugs have hit the marketplace when its label "is no longer consistent with that for the listed drug." 21 C.F.R. § 314.150(b)(10). This says nothing about matching the *approved* version of the RLD's label, just that consistency with the listed drug is key. But one could easily imagine a situation where it takes the FDA a few weeks or months to conclude that a CBE change to a listed drug's label should not be approved. This disapproval may come even though the RLD's new label has already hit the marketplace. It cannot be the case that ANDA holders must always and immediately match the contemporaneous RLD label in the marketplace, since at the time of the CBE action, later FDA disapproval remains a possibility. The duty of sameness attaches to what the FDA later approves. Cf. 78 Fed. Reg. at 67,986 (proposing to give all ANDA holders 30 days to "submit a CBE–0 supplement with conforming labeling changes *after FDA approval* of a revision to the labeling for the RLD") (emphasis added).

cess to add a new warning. (*Levine* explains why this is possible. 555 U.S. at 570–73.) This NDA RLD labeling change would create a corollary matching duty for all ANDA holders who used that drug as an RLD to obtain their own ANDA approvals. Not updating would violate the duty of sameness and perhaps also lead to state-law tort liability for inadequate warnings. See *Fulgenzi v. PLIVA, Inc.*, 711 F.3d 578, 586–87 (6th Cir. 2013) (explaining how state-law liability for inadequate warnings can be distinct from duties imposed by federal law).

But just *when* that potential liability might arise would not be clear because of the inherent lag period. FDA approval may not come until months after the CBE change has been made. For liability purposes, would the ANDA holder's 'failure to timely update' occur as soon as the NDA holder made the CBE change, or would it occur later when the FDA approved that change? When and what must ANDA holders match? The New Jersey Supreme Court has answered this question persuasively.

What matters, that court explained, are the date and substance of FDA approval. *In re Reglan Litigation*, 142 A.3d 725 (N.J. 2016). In *Reglan*, the FDA had approved new warning labels in 2004, *id.* at 729, but the plaintiffs alleged that the defendant ANDA holders had not updated their labels to match the FDA-approved warnings until 2009, long after those new warnings were issued, *id.* at 730. This claim could proceed because federal law was no longer an obstacle: the FDA had already approved a proper label for the drug. By not acting, the defendant ANDA holders had allegedly fallen below that established standard. See *id.* at 742. At the same time, the *Reglan* court also rejected the argument that the "defendant generic manufacturers had a duty to provide warnings *beyond* those

that the FDA approved for the brand name." *Id.* (emphasis added). We agree with the *Reglan* analysis. The label approved by the FDA defines an ANDA holder's duty of sameness and thus the lines of federal preemption as well.

Consider next what would happen if a drug-maker decided to create a new generic drug by copying an existing RLD product. Where would this new ANDA applicant obtain the labeling it needs to submit to the FDA for comparison under 28 U.S.C. § 355(j)? A bottle of the RLD at the nearest pharmacy? No. The agency has made clear that the FDA itself is the authoritative source of that information. Applicants must facilitate the "side-by-side comparison of the applicant's proposed labeling with the approved labeling for the reference listed drug," which is made possible by the fact that the "current approved labeling could be obtained under the Freedom of Information Act" from FDA itself. ANDA Regulations, 57 Fed. Reg. at 17,960.[10]

D. *Agreement with the Sixth Circuit in Darvocet*

As a fallback position, plaintiffs contend that even if RLDs with ANDAs approved after 1984's Hatch-Waxman Act may

[10] Approved drug labeling information is now available through a regularly-updated FDA database. See *Drug Safety Labeling Changes (SLC) Quick Reference*, U.S. Food & Drug Admin., https://www.fda.gov/Drugs/DrugSafety/ucm518488.htm (last visited Jan. 18, 2018). Recent draft guidance from the FDA says that applicants are responsible for "checking appropriate sources in order to obtain the RLD labeling," but the FDA also suggests that an applicant may resort to the marketplace to find a substitute for missing labeling only "for convenience initially." FDA, Center for Drug Evaluation and Research, Draft Guidance: Referencing Approved Drug Products in ANDA Submissions 6 n.7 (January 2017). Thus, the FDA itself is still the authoritative source for approved RLD labeling.

not take advantage of the changes-being-effected regulation, the rule should be different for Depo-T because it was approved in 1979, before the current regime was put in place. Plaintiffs argue that the intervening changes in statutes and regulations in the 1980s and 1990s that created today's approval process altered the status of pre-existing RLD ANDA holders. See Appellants' Br. at 33 n.6.

For the same reason, plaintiffs argue that we should part company from the Sixth Circuit's position on this preemption issue. With respect to generic drugs approved under the *current* regime, the Sixth Circuit concluded that "the status of an ANDA holder's product as the RLD for a given prescription drug product does not alter the ANDA holder's obligations" or make available the CBE regulation to add a new warning unilaterally. *In re Darvocet, Darvon, & Propoxyphene Prods. Liab. Litig.*, 756 F.3d 917, 923, 934 (6th Cir. 2014) (hereinafter *Darvocet*); see also *Morris v. PLIVA, Inc.*, 713 F.3d 774, 777–78 (5th Cir. 2013) (per curiam) (similar observation). *Darvocet* found preemption, and so did the district court here in applying *Darvocet*. 142 F. Supp. 3d 747, 754 (N.D. Ill. 2015).

We agree with the Sixth Circuit and reject plaintiffs' invitation to draw a distinction where one is not clearly called for. The FDA has noted that products approved prior to the 1984 Hatch-Waxman changes to federal drug laws are treated the same as ANDA approvals that came after. See 21 C.F.R. § 314.94(b) (explaining that products stemming from Drug Efficacy Study Implementation approvals are subject to today's ANDA regulations). Depo-T falls under this provision. See Appellants' Br. at 7, 10. It thus makes no difference to the preemption analysis that Depo-T was approved back in 1979.

E. *Conclusion*

In sum, the statutes, regulations, and FDA interpretations that govern the labeling requirements for drugs approved pursuant to an abbreviated new drug application (ANDA) control the outcome of this case. Those authorities, and the reading given to them by the Supreme Court in *PLIVA, Inc. v. Mensing*, indicate that there is no meaningful difference for preemption purposes between ANDA holders for reference listed drugs and those for non-RLD drugs. There is also no clear reason why the specific circumstances of the approval history of this particular drug, Depo-T, should make the result any different than in *Mensing*. Since unilateral changes to Depo-T's label were not possible, state-law claims alleging a failure to take that action are preempted.

III. *Plaintiffs' Discovery Requests*

Plaintiffs also appeal the district court's denial of further discovery into communications between the defendants and the FDA about Depo-T. As a general rule, appellate courts leave discovery to the sound discretion of the district court, so we review this decision only for an abuse of discretion. *Citizens for Appropriate Rural Roads v. Foxx*, 815 F.3d 1068, 1081 (7th Cir. 2016). We find no abuse of discretion here.

Since "preemption is a legal question for determination by courts," see *Watters v. Wachovia Bank, N.A.*, 550 U.S. 1, 20 (2007), discovery of facts may not be as vital to this inquiry as it could be to others. If plaintiffs could show that the FDA had issued an authoritative legal interpretation saying that the CBE process is in fact available to the defendants to add or strengthen a warning, that would defeat the preemption defense here under the logic of *Levine*.

To support their request for discovery, plaintiffs offer two batches of correspondence between the FDA and Upjohn in the 1990s about the labeling for Depo-T. The first set of letters, from April to July 1991, refers to Upjohn's supplemental application seeking to modify the labeling for Depo-T in light of a change in federal law: the rules implementing the Anabolic Steroids Control Act of 1990. See Supp. App. at 41–46; see also Pub. L. No. 101-647, § 1901 et seq., 104 Stat. 4851 (1990); Schedules of Controlled Substances; Anabolic Steroids, 56 Fed. Reg. 5753, 5754 (Feb. 13, 1991) (final rule promulgated by the Drug Enforcement Administration requiring such labeling for testosterone by August 27, 1991). The second batch of letters, stretching from 1994 to 1996, involves Upjohn's attempts to avoid confusion between the similar-looking cartons of Depo-T and a contraceptive injection known as Depo-Provera. See Supp. App. 52–67; Appellee App. 23 (a letter from the U.S. Department of Health and Human Services requesting Upjohn change its similar-looking drug cartons); see also 21 U.S.C. §§ 331(a), 331(b), 321(m), 352(a), and 352(f) (ANDA holders' duty to avoid misbranding and mislabeling their products).

The most those letters show is that the CBE process might have been used in the early 1990s to make Depo-T's label conform with a change in federal law, and perhaps again to avoid confusion at the request of a different federal agency. These kinds of CBE changes are not relevant to our preemption analysis because they focus on using the regulation for reasons other than adding additional warnings, the sole issue of concern here.[11] In addition, though further discovery may reveal

[11] This stands in contrast to the letter of another defendant in the underlying MDL, Auxilium, that did engage the FDA on the issue of adding

more about the *defendants'* view of the CBE regulation from past decades, it would not be likely to uncover what the plaintiffs actually need: the FDA's policy before *Mensing* was decided in 2011 about whether ANDA holders like Upjohn could have added warnings through the CBE process. The plaintiffs already have available to them the process they might need for that kind of discovery—the Freedom of Information Act, 5 U.S.C. § 552 et seq. The district court did not abuse its discretion by denying discovery on this point.

Conclusion

We AFFIRM the decisions of the district court challenged in this appeal, apart from those vacated by the separate jurisdictional order issued today.

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warnings through the CBE process. See *In re TRT*, No. 14 C 1748, 2016 WL 861213, at *4 (N.D. Ill. Mar. 7, 2016); R. 1175 at 3-4. The resulting response from the FDA, as described by the district court, further reinforces our point above that "such changes require the agency's advance approval" and could not be made unilaterally by that ANDA holder through the CBE process.