Legal Backgrounder

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Recent Rulings Establish New Beachheads for Preemption in Drug and Device Product-Liability Litigation

by James M. Beck

When *Wyeth v. Levine*, 555 U.S. 555 (2009), rejected both "goals and objectives" and "impossibility" preemption for prescription drugs, it appeared to be a Waterloo moment for these FDA-regulated products' most powerful defense. But after a very difficult period, defendants regrouped, primarily by focusing on the limitations to *Levine*'s impossibility-preemption rationale. *Levine* turned on the availability of an FDA regulatory exception that makes it possible for a manufacturer to strengthen already approved warnings without first submitting the change to the agency:

> Among other things, this 'changes being effected' (CBE) regulation provides that if a manufacturer is changing a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction' or to 'add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product,' it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

Id. (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A), (C)).

Since *Levine*, prescription-drug defendants have clawed back a considerable degree of preemption in areas beyond the reach of the FDA's CBE regulation. Defendants have also, in certain situations, overcome the hurdles created by *Levine*'s "clear evidence" standard for determining if the FDA "would not have approved" the warning a plaintiff demands had it been presented to the agency. *Id.* at 571. Several recent decisions establish new beachheads for preemption.

Gustavsen v. Alcon Laboratories, Inc., 903 F.3d 1 (1st Cir. 2018). The key to most post-*Levine* preemption is the so-called independence principle articulated in *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 623-24 (2011): "[W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes." In *Gustavsen*, the U.S. Court of Appeals for the First Circuit recognized that this independence principle applies whenever the product change a plaintiff seeks would be a "major change" under FDA regulations.

Gustavsen was a consumer class action alleging that eyedrop dispensers produced excessively large droplets. 903 F.3d at 5. Plaintiffs contended that droplets of a "proper" size would mean more doses per container, and thus a reduced price per dose. *Id*. Even if plaintiffs' economic theory made any sense, it was also preempted. To change the size of eyedrop droplets altered the drug's dosage, and a change in the dose of a prescription drug is a "major change" to the drug under the relevant FDA regulation. *See* 21 C.F.R. § 314.70(b). Anything that "dictat[ed] the size of the drops" "control[led] the drug product delivered (specifically its amount)

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to a patient." 903 F.3d at 11 (internal quotations omitted). Thus, it was a "major change."

> Critically, any major product change requires FDA pre-approval, as the court explained:
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> The [FDA] classification of the manufacturer's anticipated alteration . . . 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). . . . [I]f the change [plaintiffs] 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. Our inquiry [is] straightforward: Does the change urged by plaintiffs qualify as 'major'? If so, our work is done.

Id. at 10 (citations omitted).

Gustavsen dotted every "i" and crossed every "t" in reviewing FDA regulations, guidance, and even a preamble to support its conclusion that altering eyedrop droplets constituted a "major" change. *Id*. at 12-13. However, its legal analysis was simple and quite correct—if a common-law claim demands a product alteration that the FDA classifies as "major," then that claim is preempted.

The implications of *Gustavsen*'s equation of "major" changes to FDA-regulated products with preemption are broad. Many types of product changes, not only to prescription drugs but to medical devices as well, are considered "major" under the FDA's regulatory scheme. In *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013), the Supreme Court pointed out that "the manufacturer is prohibited from making any major changes to the 'qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application'." *Id*. at 477 (quoting 21 C.F.R. § 314.70(b)(2)(i)). The Court recognized that this was true for any drug, "whether generic or brand-name." *Id*. In addition to design claims attacking a product's "formulation" or "specifications," a number of labeling changes for prescription drugs are considered "major," and thus require prior FDA review, including:

- Changes based on postmarketing study results, including, new indications and usage.
- Pharmacoeconomic claims based on clinical studies.
- Changes to clinical pharmacology and clinical study labeling reflecting new or modified data.
- Changes based on data from preclinical studies.
- Revision of the population intended for the product's use.
- Superiority claims.
- Many changes to labeled storage conditions.[1]

Of greatest potential long-term significance, the FDA treats alterations to medical devices under the same general rubric. For "substantially equivalent" devices cleared for marketing under the § 510(k) process, FDA must review any "major modification" of device design before that change is made. 21 C.F.R § 807.81(a)(3). A "major modification" is any "change or modification in the device that could significantly affect the safety or effectiveness of the device." *Id*. Thus, any design change that could be causal in product-liability litigation—as affecting product "safety"—would also be a "major modification." Eventually the "independence principle" implied-preemption argument may be most valuable in product-liability litigation involving § 510(k) medical devices.

Byrd v. Janssen Pharmaceuticals, Inc., 2018 WL 4554490 (N.D.N.Y. Sept. 21, 2018). The independence principle of implied preemption can also defeat product-liability litigation concerning off-label use. "Off-label" ordinarily means just that—medical treatment beyond a product's FDA-labeled indications. For its part, the FDA stringently restricts on-label warnings about off-label uses. For prescription drugs, such warnings may only be

[1] FDA, CDER, "Guidance for Industry: Changes to an Approved NDA or ANDA," 2004 WL3199016 (FDA, Apr. 1, 2004), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf.

"required by the FDA," not added unliaterally. 21 C.F.R. §§ 201.80(e), 201.57(c)(6)(i). For medical devices, the FDA likewise can require warnings about risks of off-label uses on any "restricted" device.[2]

The *Byrd* decision is the first to recognize the preemptive impact of regulations requiring prior FDA approval of on-label warnings about off-label uses. The drug at issue in *Byrd* was not indicated for adolescent use. 2018 WL 4554490, at *4. Plaintiff, a minor, took the drug from 2002-2006, *id*. at *6, while a predecessor regulation provided that off-label warnings "may be required by the [FDA] if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard."[3]

The defendant in *Byrd* argued, based on this regulatory scheme, that the FDA pre-approval requirement for off-label warnings preempted common-law claims that demanded off-label warnings. The *Byrd* court was "especially persuaded by the second and third of Defendants' three general arguments." 2018 WL 4554490, at *6. The "third argument" rejected plaintiffs' contention "that manufacturers of prescription medicine can unilaterally add safety information regarding off-label [use]" as "contrary to . . . the plain language of the regulations." *Id*. (rejecting "ipse dixit" opinion of plaintiffs' expert). *Byrd* also relied upon language in the pre-2006 regulation that restricted the FDA's ability to approve off-label use warnings only if the risk was "serious." *Id*. at *6.

Because the FDA must pre-approve all off-label use warnings (or, pre-2006, off-label use warnings about "serious risks"), a state-law cause of action demanding such warnings immediately was preempted in *Byrd*:

> For all of these reasons, the Court grants Defendants' motion for judgment a matter of law. The Court notes that, while granting a summary judgment motion based on preemption might have been appropriate, . . . the issue of preemption has been clarified. . . . [I]n rendering the above-described [preemption] findings, [the court] does not accept any argument that Defendants could have warned of the risks [at issue] through other means (such as sales force communications, medical education, 'Dear Doctor' letters, regional advisory committee meetings, its website, or medical literature). . . . Nor does the Court accept any argument that, if Defendants were precluded from warning of [the risks], then they should not have permitted or encouraged its off-label use at all.

Id. at *8 (footnotes omitted).

With increasing frequency, product-liability plaintiffs have brought warning claims when their injuries were allegedly caused by off-label use of FDA-regulated products. Under the FDA's regulatory scheme, only the FDA can require warnings about risks arising from off-label use. As *Byrd* recognizes, off-label warning claims are vulnerable to preemption under the Supreme Court's "independence principle" recognized in *Mensing*.

Dolin v. GlaxoSmithKline LLC, 901 F.3d 803 (7th Cir. 2018). Perhaps the substantive area most adversely affected by *Levine* was preemption arguments made by manufacturers of selective serotonin reuptake inhibitors (SSRI) anti-depressants in suicide cases. After *Levine*, courts nearly unanimously rejected "clear evidence" arguments regarding these drugs.[4] It took, literally, years, before an SSRI defendant established a regulatory

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[2] All prescription-only medical devices are "restricted devices. 21 U.S.C. § 360j(e)(1)(B)(2). *See* 21 C.F.R. §§ 895.25(b), 814.82(a) (FDA power to impose post-marketing labeling requirements); 21 C.F.R. § 807.3(i) (FDA power to impose "requirements" on all types of devices).

[3] *Id*. at *6 n.3 (quoting former 21 C.F.R. § 201.57(e) (2006)). The "serious risk" language has since been deleted.

[4] *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 395-96 (7th Cir. 2010); *Cross v. Forest Laboratories*, 102 F. Supp. 3d 896, 900-01 (N.D. Miss. 2015); *Shipley v. Forest Laboratories, Inc.*, 2015 WL 4199739, at *10-11 (D. Utah July 13, 2015); *Bennett v. Forest Laboratories*, 2015 WL 1418444, at *4-5 (M.D. Fla. Mar. 27, 2015); *Muzichuck v. Forest Laboratories, Inc.*, 2015 WL 235226, at *8 (N.D.W. Va. Jan. 16, 2015); *Koho v. Forest Laboratories, Inc.*, 17 F. Supp. 3d 1109, 1117-18 (W.D. Wash. 2014); *Wells v. Allergan, Inc.*, 2013 WL 389147, at *6-7 (W.D. Okla. Jan. 31, 2013); *Schilf v. Eli Lilly & Co.*, 2010 WL 3909909, at *4 (D.S.D. Sept. 30, 2010); *Baumgardner v. Wyeth, Inc.*, 2010 WL 3431671, at *1 (E.D. Pa. Aug. 30, 2010); *Aaron v. Wyeth*, 2010 WL 653984, at *5-6 (W.D.

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history sufficiently solid to convince a skeptical court that the regulatory record included "clear evidence"—as required under *Levine*—showed that the FDA would not have required plaintiff's warning. That finally happened in *Dolin*.

"To change the label, [defendant] needed either FDA permission or newly acquired information that supported a strengthened warning under the CBE regulation."[5] Neither existed on the record in *Dolin*. On the question of permission, the critical period was in 2007. In 2006 the defendant added a drug-specific suicide warning. *Id*. at 813. However, in 2007, "the FDA completed its own analysis of the same data and ordered [defendant] to remove that warning." *Id*. Instead the FDA imposed a uniform suicide warning on all SSRIs. *Id*. at 813-14. After the FDA's action, the defendant "followed up with four requests to re-consider and to allow [its 2006] warning. Each time, the FDA told [defendant] not to add the [drug]-specific warning." *Id*. at 814.

Liability could not overcome the FDA's removal order and the agency's four subsequent refusals to reconsider. A drug-specific argument nitpicking the structure of defendant's label failed as an "unreasonable interpretation" of the FDA's actions. *Id*. at 814. Similarly, a claim that defendant "could have followed up with a formal meeting with the FDA" failed—it was indistinguishable from an argument rejected by the Supreme Court in *Mensing*:

> [*Mensing*] rejected the plaintiff's argument that the generic manufacturer could have asked the FDA to change the brand-name label. . . . That is what plaintiff's second **argument amounts to. The preemption analysis asks only whether [defendant] could have added the adult-suicidality warning through the CBE regulation, not whether [it] might have been able to persuade the FDA to change its mind in a formal meeting.

Id. (citation omitted).

On the second *Levine* prong—newly acquired information—there was none: "[U]ndisputed evidence shows that the FDA was aware of the nature of the data it received from [defendant]." *Id*. at 815. Another article "was not new analysis" since it was based on the same information GSK had submitted to the FDA in 2006. *Id*. at 815-16. Thus, clear evidence supported preemption. "The FDA said no, repeatedly." *Id*. at 816.

Dolin means that implied preemption, under the *Levine* clear-evidence standard, still exists in litigation over SSRIs and adult suicide. The FDA's classwide labeling, that "does not warn of any association with an increased risk of suicide in adults older than 24," remains the FDA standard to this day. *Id*. at 810. Thus, one of the earliest and most contentious *Levine* preemption battlegrounds is poised to return, as the FDA's position rejecting the additional warnings plaintiffs argue for has been clarified with the passage of time.

Conclusion. The Supreme Court in *Levine* based its preemption analysis on the FDA's CBE regulation, rather than on a reasoned analysis of circumstances under which product liability did or did not interfere with the FDA's goals and objectives. The CBE regulation was not created to define preemption, and thus not designed to bear the preemptive burden *Levine* placed upon it. The unintended consequences of *Levine* thus support preemption in a variety of circumstances where the "narrow" CBE regulation does not apply—not only generic drugs, but also "major" changes (*Gustavsen*) and off-label use warnings (*Byrd*). Further, courts have been clarifying *Levine*'s "clear evidence" language, allowing defendants, as in *Dolin*, to marshal regulatory facts that meet even this demanding standard.

Pa. Feb. 19, 2010); *Forst v. SmithKline Beecham Corp.*, 639 F. Supp. 2d 948, 954 (E.D. Wis. 2009); *Van Dyke v. Smithkline*, 2009 WL 10671936, at *10 (D. Wyo. Mar. 27, 2009). *But see Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264, 1271-75 (W.D. Okla. 2011) (finding clear evidence preemption).

[5] *Dolin*, 901 F.3d at 807. The FDA's CBE regulation "allows [drug] manufacturers to change a label to 'reflect newly acquired information' if . . . the changes 'add or strengthen a . . . warning' for which there is 'evidence of a causal association'." *Id*. at 806 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)).

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