FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

MARGARITA GAETA, as guardian ad litem for A.G., a minor child; AUGUSTINE GAETA, *Plaintiffs-Appellants,* v. PERRIGO PHARMACEUTICALS COMPANY; BASF CORPORATION, *Defendants-Appellees.*	No. 09-15001 D.C. No. 5:05-cv-04115-JW OPINION

Appeal from the United States District Court
for the Northern District of California
James Ware, District Judge, Presiding

Argued and Submitted
October 6, 2010—San Francisco, California

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Before: David R. Thompson, Ferdinand F. Fernandez and
Barry G. Silverman, Circuit Judges.

Opinion by Judge Thompson

COUNSEL

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OPINION

THOMPSON, Senior Circuit Judge:

Plaintiffs-appellants Margaret Gaeta, as guardian ad litem for A.G., a minor child, and Augustine Gaeta (collectively, "the Gaetas") appeal the district court's grant of summary judgment in favor of Perrigo Pharmaceutical Company. The district court determined that the Gaetas' state law failure-to-warn claims against Perrigo, a manufacturer of a generic version of ibuprofen, were preempted under federal law. Subsequently, the Supreme Court decided *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), and determined that state law failure-to-warn claims against *brand name* manufacturers were not preempted by federal law. The district court, however, denied the Gaetas' motion for reconsideration, concluding that *Levine* does not govern whether federal law preempts similar claims against *generic* manufacturers.

Since then, two Courts of Appeals and all of the district courts to consider the issue have held otherwise, using the rationale underlying *Levine* to find that federal law does not preempt state law failure-to-warn claims against generic manufacturers, provided there is no "clear evidence" that the FDA would not have approved the proposed stronger warning. We agree and hold that the district court erred in applying federal preemption. Accordingly, we reverse and remand.

I

On June 3, 2004, A.G. had two benign moles removed in a surgical procedure. During the procedure, A.G. received Halothane, an anesthetic known to be "hepatotoxic"—that is, to cause liver failure in certain circumstances. After the surgery, A.G. was discharged with a prescription for ibuprofen and instructions to take one 400mg tablet once every six hours as needed for pain. Instead, A.G.'s parents purchased Perrigo's generic over-the-counter ("OTC") ibuprofen at 200mg per tablet. For the next four days, A.G. took 400mg of the generic ibuprofen every six to eight hours.

On June 11, 2004, A.G. developed a fever and was seen by his pediatrician, who prescribed prescription-strength ibuprofen (400mg). However, A.G.'s condition continued to worsen, and on June 13, 2004, he was referred to the emergency room with a diagnosis of septic shock, dehydration, and liver failure. He was later transferred to Stanford University Hospital for a liver transplant, which took place on June 15, 2004. A.G. also developed other complications, and he eventually required amputation of necrotic tissue on his fingers and toes.

The Gaetas filed suit against Perrigo and several other manufacturers of generic ibuprofen, alleging defective design, defective marketing, breach of express and implied warranty, negligence and gross negligence, and deceit by concealment.[1] Prevalent in all of the Gaetas' claims is the allegation that the generic manufacturers failed to warn prescribing physicians and consumers of the increased risk of acute liver injury and renal (i.e., kidney) failure when ibuprofen is taken concurrently with other drugs known to be hepatotoxic.

[1]The Gaetas have either settled with or dismissed all of the manufacturers except Perrigo.

Perrigo moved for summary judgment on preemption grounds, arguing that the Gaetas' state law failure-to-warn claims conflicted with FDA regulations relating to the labeling and marketing of generic drugs. The district court agreed, and concluded that the Gaetas' claims were preempted because a generic manufacturer could not comply with the heightened state law warning requirements without running afoul of the FDA regulations requiring generic drug labels to conform to the approved labeling for brand name drugs. The district court granted summary judgment in favor of Perrigo, and the Gaetas appealed.

The Supreme Court subsequently decided *Levine*, 129 S. Ct. 1187. In light of *Levine*, the Gaetas obtained a limited remand from this court to allow the district court to consider a post-judgment motion for reconsideration. The district court, however, denied the motion for reconsideration, concluding that the Court's holding in *Levine* that the FDA regulations do not preempt state tort law claims for inadequate labeling against *brand name* manufacturers does not govern whether the FDA regulations preempt similar claims against *generic* manufacturers.

II

We review de novo an order granting summary judgment. *Lopez v. Smith*, 203 F.3d 1122, 1131 (9th Cir. 2000) (en banc). We must determine "whether, viewing the evidence in the light most favorable to the nonmoving party, there are any genuine issues of material fact and whether the district court correctly applied the relevant substantive law." *Id.* (citation omitted).

III

[1] This appeal presents an issue of first impression for our court. We must determine what effect, if any, the Supreme Court's decision in *Levine* has on the question whether appli-

cable FDA regulations preempt state tort law claims for inadequate labeling against generic—as opposed to brand name—manufacturers. In resolving this question, we consider a brief history of federal drug regulation and labeling.

A. The FDA's Regulation of Drugs

In the 1930's, Congress became "increasingly concerned about unsafe drugs and fraudulent marketing," *Levine*, 129 S. Ct. at 1195, and enacted the Federal Food, Drug, and Cosmetic Act ("FDCA"). *See* 21 U.S.C. § 301 *et seq.* The FDCA required every manufacturer to submit a new drug application ("NDA"), including reports of investigations and specimens of proposed labeling, to the FDA before any new drug could be marketed and sold to the public. 21 U.S.C. § 355(b). In 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer. *Levine*, 129 S. Ct. at 1195. These amendments, which are still in effect, require the manufacturer to demonstrate that its drug is "safe" and "effective" before the drug can be distributed. *Id.*; *see also* 21 U.S.C. § 355(b). Once the drug covered by the NDA is approved for safety and effectiveness, that drug—also referred to as the "listed drug"—may be sold to consumers under the NDA holder's brand name.

A less demanding approval process applies to manufacturers seeking to market generic drugs. In 1984, Congress passed the Hatch-Waxman Amendments to the FDCA, which provided that once a brand name drug's NDA is approved and the drug is officially listed by the FDA, any manufacturer may seek permission to market a generic version of that drug by submitting an abbreviated NDA ("ANDA"). *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984). Under the Hatch-Waxman Amendments, generic manufacturers need not repeat the clinical work of their brand name counterparts, but rather must establish that except for enumerated differences irrelevant here, their drug is the "same as" the brand name drug

that has already been approved by the FDA as to active ingredients, route of administration, dosage form, strength, and conditions of recommended use specified on the label. 21 U.S.C. § 355(j)(2)(A). By avoiding unnecessary duplication of previously-performed clinical trials, Congress sought to accelerate the availability of low-cost drugs, thereby resulting in significant cost savings to the American public.[2]

ANDA applicants must also show that the labeling proposed for a new generic drug is the "same as" the labeling approved for the listed drug. 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G). At any time after a new generic drug is approved, the FDA reserves the right to withdraw approval if it determines that the generic drug's labeling is "no longer consistent" with that of the listed drug. 21 C.F.R. § 314.150(b)(10). Moreover, the FDCA prohibits all manufacturers from distributing a "misbranded" drug, 21 U.S.C. § 331(a)-(b), including a drug whose "labeling is false or misleading in any particular." *See* 21 U.S.C. § 352(a). The FDA has enforcement mechanisms to ensure that drugs with misleading labels are taken off the market. *See* 21 U.S.C. §§ 333, 355(e).

B. The Supreme Court's Decision in *Wyeth v. Levine*

In *Levine*, the plaintiff, Diana Levine, brought suit against a drug manufacturer, Wyeth, when she developed gangrene after receiving an IV-push injection of Phenergan, Wyeth's brand name for an antihistamine used to treat nausea. 129 S. Ct. at 1191. Levine asserted state tort law claims against Wyeth alleging that Phenergan's labeling was defective because, although it warned of the danger of gangrene and amputation following inadvertent intra-arterial injection, the label failed to warn against the use of the IV-push method for

[2]For example, generic drugs saved American consumers between approximately $8 billion and $10 billion in 1994. CONGRESSIONAL BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 13 (July 1998).

administering the drug, which posed a higher risk than the IV-drip method. *Id.* at 1191-92.

The Supreme Court upheld the trial court's refusal to overturn on preemption grounds the jury's verdict in favor of Levine. *Id.* at 1204.

Wyeth contended it would have been impossible for it to comply with the state-law duty to modify Phenergan's labeling without violating federal law. *Id.* at 1196. The Court rejected this argument, concluding that because FDA regulations permit drug manufacturers to make certain changes to their labels without prior FDA approval, Wyeth could have met its state-law obligation to provide additional warnings without violating FDA labeling requirements. *Id.* at 1196-99. Specifically, the Court determined that Wyeth could have utilized the FDCA's changes being effected ("CBE") regulation, which permits drug manufacturers to change a label, without prior FDA approval, to "add or strengthen a contraindication, warning, precaution, or adverse reaction," 21 C.F.R. § 314.70(c)(6)(iii)(A) (2004), or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," 21 C.F.R. § 314.70(c)(6)(iii)(C). *Levine*, 129 S. Ct. at 1196-99.

Next, the Court concluded there was no merit to Wyeth's contention that Levine's state tort claims were preempted because they interfered with Congress' purpose to entrust the FDA with making drug labeling decisions. *Id.* at 1199. In doing so, the Court noted that Congress had repeatedly declined to preempt state law in the field of prescription drugs. *Id.* at 1200. The Court also concluded that the FDA's unilateral assertion of broad preemption power in this area, *see* 71 Fed. Reg. 3922, 3934-35 (Jan. 24, 2006), was entitled to no weight. *Id.* at 1200-04. According to the Court, because manufacturers have "superior access to information" about their drugs than does the FDA, especially in the post-

marketing phase as new risks emerge, they "bear primary responsibility for their drug labeling at all times." *Id.* at 1202.

[2] The focal issue in this appeal is whether the Court's holding in *Levine*—that the federal regulatory regime governing pharmaceuticals does not preempt state law failure-to-warn claims against brand name manufacturers—extends with equal force to claims against generic manufacturers.[3] As explained below, today we join the Fifth and Eighth Circuits in concluding that, while not dispositive, *Levine* does foreshadow a similar disposition in this case. *See Demahy v. Actavis, Inc.*, 593 F.3d 428, 430 (5th Cir. 2010), *cert. granted*, 78 U.S.L.W. 3745 (U.S. Dec. 10, 2010) (No. 09-1501); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 607 (8th Cir. 2009), *cert.* granted, 78 U.S.L.W. 3522 (U.S. Dec. 10, 2010) (No. 09-993), *and cert. granted*, 78 U.S.L.W. 3523 (U.S. Dec. 10, 2010) (No. 09-1039).

C. Preemption Analysis

In considering a federal preemption defense, we are guided by two important considerations. First, " 'the purpose of Congress is the ultimate touchstone in every pre-emption case.' " *Levine*, 129 S. Ct. at 1194 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Second, we must apply the presumption against preemption, especially when "Congress has legislated . . . in a field which the States have traditionally occupied." *Id.* (quoting *Lohr*, 518 U.S. at 485) (internal quotation marks omitted). As the Supreme Court explained, "[w]e rely on the presumption because respect for the States as 'independent sovereigns in our federal system' leads us to assume that 'Congress does not cavalierly pre-empt state-law causes of action.' " *Id.* at 1195 n.3 (quoting *Lohr*, 518 U.S. at 485).

[3]We note that the issues of causation and whether there was additional evidence indicating the need for hepatotoxicity warnings with the OTC use of ibuprofen are still highly disputed in this case. We leave those issues for the district court to decide in the first instance.

[3] Under the Supremacy Clause, U.S. CONST. art. VI, cl. 2, Congressional intent to preempt state law can either be expressed in statutory language or implied from the scheme of federal regulation. *Hillsborough Cnty., Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712-13 (1985). Implied preemption comes in two forms: field and conflict preemption. Field preemption occurs when the federal regulation is sufficiently comprehensive to leave no room for supplementary state regulation. *Id.* at 713. Conflict preemption, in turn, arises when: (1) " 'compliance with both federal and state regulations is a physical impossibility,' " or (2) "state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.' " *Id.* (citations omitted). The conflict might be with a federal statute or an "agency regulation with the force of law." *Levine*, 129 S. Ct. at 1200.

In the present case, Perrigo contends the Gaetas' claims are conflict preempted because it is impossible for Perrigo to comply with both the state-law duties to warn and the federal regulatory regime governing generic drugs. Alternatively, Perrigo contends that the Gaetas' state law claims are conflict preempted because they obstruct the full accomplishment of the purposes and objectives of Congress in enacting the Hatch-Waxman Amendments. We reject both contentions.

1. There is no impossibility of compliance.

Impossibility preemption is "a demanding defense." *Levine*, 129 S. Ct. at 1199. In asking us to uphold the district court's finding of preemption, Perrigo in effect asks us to disregard the underlying reasoning of *Levine* and to create an intercircuit split with respect to generic manufacturers' liability for inadequate labeling. We decline to do so.

[4] We agree with the Gaetas, and with our two sister circuits, that the FDCA provides generic manufacturers with at least three separate mechanisms by which they can discharge

their state-law duty to warn of additional risks associated with their products: (a) the CBE process approved by the Supreme Court in *Levine*; (b) the "prior approval" process; and (c) by asking the FDA to send "Dear Doctor" warning letters to health care professionals.

Initially, there is no dispute between the parties that the Hatch-Waxman Amendments require an ANDA *applicant* to use a drug label that is the "same as" that approved for the listed drug. *See* 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G). The only dispute is whether ANDA *holders* must similarly comply with that requirement *after* their applications have been approved. Perrigo contends that they do and points to 21 C.F.R. § 314.150(b)(10), which allows the FDA to withdraw approval if the agency finds that the drug's labeling is "no longer consistent" with that for the listed drug, and 21 U.S.C. § 352(a), which prohibits the manufacture and distribution of any "misbranded" drug. However, the fact that a generic drug's label must remain "consistent" with that for the listed drug does not mean that the two labels must be "identical." In other words, just because a generic drug's label has stronger warnings than those on the label of its brand name counterpart does not mean the two labels lack consistency. For example, the Supreme Court in *Levine* found it "difficult to accept" that the FDA would bring an enforcement action against a manufacturer for strengthening a warning on a drug's label. 129 S. Ct. at 1197. Similarly, the Court noted that a drug is not misbranded "simply because the manufacturer has altered an FDA-approved label." *Id.* Instead, "the misbranding provision focuses on the substance of the label" and in fact "*proscribes* labels that fail to include 'adequate warnings.' " *Id.* (quoting 21 U.S.C. § 352(f)) (emphasis added); *accord Demahy*, 593 F.3d at 439 ("[R]ather, the misbranding provisions concern the accuracy of the label's substance and the adequacy of its warnings . . . ." (citations omitted)).

[5] Indeed, the regulatory framework makes clear that generic manufacturers, just like their brand name counter-

parts, must take specific steps when they learn of new risks associated with their products. Thus, both sets of manufacturers must record and report to the FDA certain adverse effects. *See* 21 C.F.R. § 314.80(a), (c) (NDA holders); 21 C.F.R. § 314.98(a) (ANDA holders). Similarly, both sets of manufacturers must submit annual reports that include, *inter alia*, a "brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and a "brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study." 21 C.F.R. § 314.81(b)(2)(I) (NDA holders); 21 C.F.R. § 314.98(c) (ANDA holders).

[6] Based on these adverse reports, drug manufacturers "shall" revise their drug labeling to include a warning "as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.57(e) (2004).[4] And even though the FDA is the final arbiter of whether any such labeling revision is appropriate, the "primary responsibility" for the label's adequacy always remains with the drug manufacturer. *Levine*, 129 S. Ct. at 1202; *see also id.* at 1197-98 ("[I]t has remained a central premise of federal drug regulation that the manufacturer bears the responsibility for the content of its label at all times.").

i. A generic manufacturer can utilize the CBE process to make changes to its label without any prior approval by the FDA.

Generally speaking, FDA approval is necessary before a manufacturer may change a drug label. 21 C.F.R. § 314.70(b)(2)(v)(A). As one exception, however, the CBE

[4]This version of the regulation was in effect when A.G.'s injury took place. Today, this provision is codified in 21 C.F.R. § 201.80(e).

provision allows a drug manufacturer to make a label change that becomes effective immediately upon the FDA's receipt of the supplemental application for the change. 21 C.F.R. § 314.70(c)(6)(iii). A drug manufacturer can utilize the CBE process to strengthen its warnings when doing so is necessary "to reflect newly acquired information." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). As the Court explained in *Levine*, in this context, the "newly acquired information" is not limited to new data, but "also encompasses 'new analyses of previously submitted data.' " 129 S. Ct. at 1197 (quoting 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008)). As such, this rule "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Id.*

[7] Nothing in the text of the Hatch-Waxman Amendments forbids an ANDA holder from utilizing the CBE process. Indeed, the opposite is true. The CBE provision is contained in 21 C.F.R. § 314.70, which is located in Subpart B of the Regulations (entitled, "Applications") and which admittedly deals only with applications for the listed drugs. However, § 314.70 is expressly made applicable to ANDA holders by operation of 21 C.F.R. § 314.97, which is located in Subpart C of the Regulations (entitled, "Abbreviated Applications") and provides that ANDA applicants "*shall comply* with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application" (emphasis added).[5]

[5]Relying on *Morris v. Wyeth, Inc.*, 642 F. Supp. 2d 677 (W.D. Ky. 2009), *appeal docketed*, No. 09-5509 (6th Cir. Apr. 27, 2009), Perrigo proposes an alternate way to read 21 C.F.R. § 314.97. According to this view, "§ 314.97 merely states that when a brand [name] manufacturer utilizes § 314.70, then so too must the generic manufacturer make that same change to its corresponding drug's label." *Morris*, 642 F. Supp. 2d at 685 (denying reconsideration of the court's prior order finding plaintiff's failure-to-warn claims against generic manufacturers to be preempted). In other words, according to Perrigo, § 314.97 is merely a restatement of the initial requirement *prior to approval* that the labeling for a generic drug

All but one of the courts to consider this issue after *Levine* have concluded that the CBE process is available to generic manufacturers on the same terms as to brand name manufacturers.[6] Indeed, except for the district court's decision in this case, Perrigo cannot point to any post-*Levine* decision con-

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must be the "same as" that of the brand name equivalent, no more and no less.

This, however, is a very strained reading of § 314.97. As the Fifth Circuit observed in addressing the same question, had the FDA intended to deny generic manufacturers access to the CBE process despite § 314.97's plain language, we might expect the FDA to say so, either in § 314.97 or § 314.70. *See Demahy*, 593 F.3d at 441. The FDA has not done so, however, and we decline to imply such a constricting limitation ourselves. Rather, on the face of the regulations in effect, generic manufacturers must comply with the provisions of § 314.70 and maintain adequate warnings. *See Demahy*, 593 F.3d at 441-42; *Mensing*, 588 F.3d at 611.

[6]*See, e.g.*, *Demahy*, 593 F.3d at 439-41 (concluding that the CBE process is available to generic manufacturers); *Dorsett v. Sandoz, Inc.*, 699 F. Supp. 2d 1142, 1160-62 (C.D. Cal. 2010) (same); *Munroe v. Barr Labs., Inc.*, 670 F. Supp. 2d 1299, 1302-03 (N.D. Fla. 2009) (same); *Bartlett v. Mut. Pharm. Co.*, 659 F. Supp. 2d 279, 296-99 (D.N.H. 2009) (same); *Stacel v. Teva Pharm., USA*, 620 F. Supp. 2d 899, 905 (N.D. Ill. 2009) (same). The Fourth Circuit reached a similar conclusion more than 15 years ago. *See Foster v. Am. Home Prods. Corp.*, 29 F.3d 165, 170 (4th Cir. 1994) ("Although generic manufacturers must include the same labeling information as the equivalent name brand drug, they are also permitted to add or strengthen warnings and delete misleading statements on labels, even without prior FDA approval." (citing 21 C.F.R. § 314.70 (1993))).

The only post-*Levine* case to consider the issue and reach a different conclusion was the district court's decision in this case. *See Gaeta v. Perrigo Pharm. Co.*, 672 F. Supp. 2d 1017, 1021-22 (N.D. Cal. 2009). In addition, on the day *Levine* was decided, Judge Russell of the Western District of Kentucky entered minute orders reaffirming in light of *Levine* his findings of preemption of warning claims in three related cases involving generic Reglan. *See Smith v. Wyeth, Inc.*, No. 5:07-CV-18-R, 2009 WL 736208 (W.D. Ky. Mar. 4, 2009); *Morris v. Wyeth, Inc.*, No. 1:07-CV-176-R, 2009 WL 736200 (W.D. Ky. Mar. 4, 2009); *Wilson v. Wyeth, Inc.*, No. 3:07-CV-00378-R, 2009 WL 736198 (W.D. Ky. Mar. 4, 2009). These three cases are currently in a consolidated appeal before the Sixth Circuit.

cluding otherwise.[7] Neither can Perrigo point to any authoritative statement from the FDA to the contrary. While previously Perrigo could rely on the FDA's assertion that "under existing preemption principles, FDA approval of labeling under the act . . . preempts conflicting or contrary State law," 71 Fed. Reg. 3922, 3934, that pronouncement is entitled to no weight after *Levine*. *See* 129 S. Ct. at 1201 (finding FDA's view on preemption unsupported by evidence and "inherently suspect," and concluding that it "does not merit deference"). Similarly, Perrigo receives little help from a footnote in the FDA's 2008 proposed rule to amend § 314.70, which provides:

> CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. See 21 CFR 314.150(b)(10); see also 57 FR 17950, 17953, and 17961.

73 Fed. Reg. 2848, 2849 n.1 (Jan. 16, 2008). As Perrigo itself concedes, the final version of the rule omits this footnote's language. *See generally* 73 Fed. Reg. 49603 (Aug. 22, 2008). Having been abandoned, the FDA's earlier position is "deprived of all claim to deference[ ] by the fact that it is no longer the agency's position." *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 327 (2008); *accord Demahy*, 593 F.3d at 444.

[7]In reaching its conclusion, the district court in this case relied on an apparent "split of opinion" among pre-Levine cases. *See Gaeta*, 672 F. Supp. 2d at 1021 & n.4. However, of the two decisions cited by the district court for the proposition that "a generic drug manufacturer may not unilaterally strengthen a drug label without prior FDA approval," *id.* at 1021 n.4, one has since been reversed on appeal, *see Mensing v. Wyeth*, 562 F. Supp. 2d 1056 (D. Minn. 2008), *rev'd*, 588 F.3d 603, and the other relied on the first in reaching its conclusion, *see Morris v. Wyeth*, 582 F. Supp. 2d 861, 867-68 (W.D. Ky. 2008), *reconsideration denied*, 642 F. Supp. 2d 677, *appeal docketed*, No. 09-5509 (6th Cir. Apr. 27, 2009). Accordingly, at this stage, these decisions provide little, if any, support for the district court's conclusion in this case.

Perrigo's arguments in opposition are not persuasive. For example, Perrigo argues that because it has never received, nor attempted to withhold, any information suggesting the use of its product contributed to or caused liver damage, "there was nothing [for it] to report to the FDA to support plaintiffs' proposed label change." Underlying the Gaetas' claims, however, are allegations that Perrigo *should have* followed—but *did not*—the same record keeping and reporting of adverse drug experiences post-marketing that brand name manufacturers must undertake. *See* 21 C.F.R. § 314.98. As part of that record keeping, the FDA requires ANDA holders to "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA." *See* 21 C.F.R. §§ 314.80(b), 314.98(a). And if any new information becomes available, the FDA requires ANDA holders to report what actions they have taken or intend to take as a result of this information, "for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study." 21 C.F.R. § 314.81(b)(2)(I); 21 C.F.R. § 314.98(c).

[8] Similarly, Perrigo argues that any claim that it failed to fulfill its duty to supply information to the FDA is a question for the FDA and not the court, and as such is preempted under *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-51 (2001) (finding plaintiffs' state-law "fraud-on-the-FDA" claims to be preempted). *Buckman*, however, is not applicable in this context. The question before us is not whether Perrigo provided inaccurate or incomplete information to the FDA, but rather whether it complied with its post-marketing obligations to warn consumers and health care professionals about additional risks associated with its product. Because these claims are based on Perrigo's alleged violation of its state-law duties rather than an alleged violation of the FDCA itself, they are not preempted under *Buckman*.

ii. A generic manufacturer can also utilize the "prior approval" process to propose a labeling change to the FDA that, if accepted, would be imposed uniformly on both sets of manufacturers.

Even were the CBE process unavailable to generic manufacturers, nothing in the FDCA or the Hatch-Waxman Amendments prohibits such a manufacturer from proposing a label change through the "prior approval" process. *See* 21 C.F.R. § 314.70(b)(2)(v). Unlike the CBE process, the "prior approval" process requires the FDA's approval of the supplemental application before the change can be effected. *Id.* Moreover, by using the prior approval process, a generic manufacturer would not have to worry about its labeling not being "consistent" with that of the listed drug because, if the FDA were to accept the proposed change, it would be imposed uniformly on both sets of manufacturers. *See* 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992).

[9] Indeed, it appears the FDA itself envisioned the possibility that ANDA holders would utilize the "prior approval" process to suggest new warnings to the FDA. Thus, in its commentary submitted in connection with the 1992 final rule, the FDA expressly stated that "[a]fter 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." *Id.* (emphases added). Nothing prevented Perrigo from seeking a prior approval from the FDA for a label change.

iii. A generic manufacturer can also request that the FDA send "Dear Doctor" warning letters to health care professionals.

[10] In addition to proposing a label change, Perrigo could have suggested that the FDA send a "Dear Doctor" letter to heath care professionals, warning them of the risks associated

with using ibuprofen concurrently with other drugs known to be hepatotoxic. *See* 21 C.F.R. § 200.5.

When the FDA first adopted its labeling regulations, well before the Hatch-Waxman Amendments, it made clear that the labeling requirements "do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered." 44 Fed. Reg. 37434, 37447 (June 26, 1979). Although such letters are considered regulated "labeling," *see* 21 C.F.R. § 202.1(*l*)(2), Perrigo could have asked the FDA to send them on its behalf. *See* 21 U.S.C. § 355-1(i)(2)(A) (providing that the FDA will send a letter to health care providers on behalf of an ANDA holder if such letter is a necessary part of a risk evaluation and mitigation strategy).

[11] As *Levine* reaffirmed, drug manufacturers bear primary responsibility for maintaining their labels consistent with safe and effective use of their products. In the present case, Perrigo could have used at least one of the above three mechanisms to warn consumers and health care professionals of the risks associated with using ibuprofen concurrently with other drugs known to be hepatotoxic. Accordingly, compliance with both the state-law duty to warn and federal law was not impossible.

2. There is no "clear evidence" that the FDA considered and rejected stronger warnings than those proposed by the Gaetas.

[12] Alternatively, to show that compliance was impossible, Perrigo argues the FDA considered and rejected the liver warnings that the Gaetas claim Perrigo should have provided. In *Levine*, the Supreme Court left open the possibility that there could be preemption if a manufacturer was able to demonstrate, by *clear evidence*, that the FDA would not have approved the change to the drug's label proposed by the plaintiff. 129 S. Ct. at 1198. The Court, however, did not clarify

what would amount to "clear evidence." Rather, the only guidance this court has is that the evidence presented in *Levine* was insufficient to meet the clear evidence standard. *See, e.g.*, *Mason v. Smithkline Beecham Corp.*, 596 F.3d 387, 391-92 (7th Cir. 2010) (using *Levine* as an "intellectual anchor" to judge whether the evidence presented by the brand name manufacturer amounted to "clear evidence"). Accordingly, if there is evidence in this case less compelling than there was in *Levine*, that the FDA would not have approved the applicable label change, there is no preemption.

In *Levine*, Wyeth appealed from the jury's determination that it had failed to provide an adequate warning that directly injecting Phenergan into a patient's vein creates a significant risk of catastrophic consequences. 129 S. Ct. at 1190-91. In determining whether "clear evidence" of the FDA's consideration of the warning was presented, the Court focused on whether Wyeth "attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA." *Id.* at 1198.

The Court noted that in 1988, Wyeth did propose different language for Phenergan's warning about intra-arterial injection, adapted from revisions the FDA proposed in 1987, but the FDA instructed Wyeth to retain the wording in its existing label. *Id.* at 1198 n.5. The FDA apparently "did not regard the proposed warning as substantively different" from the FDA-approved warning. *Id.* The Court also noted that there was no evidence in the record that either the FDA or Wyeth gave more than "passing attention" to the precise issue in that case —i.e., the difference between the IV-drip and the more dangerous IV-push administration of Phenergan.[8] *Id.* at 1198-99.

[8]Indeed, the *Levine* majority criticized the dissent for "creatively paraphras[ing] a few FDA orders" and thereby "conflating warnings about IV-push administration and intra-arterial injection to suggest greater agency attention to the question." 129 S. Ct. at 1199 n.6 (internal citations omitted).

Finally, the Court observed that Wyeth did not argue "that it supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." *Id.* at 1199. Accordingly, the Court concluded that Wyeth failed to present clear evidence that the FDA would have prevented it from adding a stronger warning about the IV-push method of intravenous administration. *Id.*

With this in mind, we turn to the evidence presented by Perrigo in this case. In the United States, ibuprofen has been used as a prescription drug for the treatment of osteoarthritis and rheumatoid arthritis since 1974. 67 Fed. Reg. 54139, 54139 (Aug. 21, 2002). The FDA approved the use of 200mg ibuprofen as an OTC drug through the NDA process in 1984, and as a generic drug in 1986. *Id.* at 54140-41. In 1987, Perrigo obtained approval to market its generic OTC ibuprofen.

In 2002, in response to a citizen petition, the FDA engaged in a detailed review regarding the safety of ibuprofen.[9] *Id.* at 54141-48. Based on this review, the FDA proposed adding warnings to alert individuals of the potential for renal and gastrointestinal problems associated with ibuprofen. *Id.* at 54148. In contrast, the FDA found there was limited clinical data available to estimate the prevalence of hepatotoxicity with OTC doses of ibuprofen. *Id.* at 54145-46. Accordingly, the FDA concluded that there was "no need to propose a hepatitis warning *at this time*." *Id.* at 54146 (emphasis added).

Then, in 2006, the FDA considered what types of warnings should be included for OTC internal analgesic, antipyretic, and antirheumatic drug products, including ibuprofen. *See* 71 Fed. Reg. 77314 (Dec. 26, 2006). Based on its review, the

[9]The citizen petition sought to have ibuprofen included as a generally recognized safe and effective analgesic/antipyretic active ingredient for OTC use. 67 Fed. Reg. 54139, 54140. The petition requested warnings "specific for the OTC use of ibuprofen," but did not request a specific warning for liver toxicity. *See id.*

FDA concluded that additional warnings were necessary regarding: (1) hepatotoxicity associated with acetaminophen, and (2) gastrointestinal bleeding and renal toxicity associated with aspirin and other nonsteroidal anti-inflammatory drugs. *See id.* at 77316, 77323-24, 77327-28, 77331-33, 77340. No warnings specific to hepatotoxicity due to ibuprofen use were proposed or considered by the FDA at that time.

[13] The above two FDA reviews do not amount to "clear evidence" that the FDA would not have approved the warnings suggested by the Gaetas. Nowhere does Perrigo point to any evidence that the FDA was presented with and actually considered the risk of hepatotoxicity due to concomitant use of ibuprofen and other drugs known to be hepatotoxic, which is the specific warning requested by the Gaetas in this case. *See Levine*, 129 S. Ct. at 1198 (focusing on whether the drug manufacturer "attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA"). Rather, the only time the FDA actually considered hepatotoxicity associated with the use of ibuprofen—as opposed to acetaminophen—the FDA expressly concluded that there was "no need to propose [such a] warning *at this time*." 67 Fed. Reg. 54139, 54146 (emphasis added). It is a stretch to contend, as Perrigo does, that this amounts to clear evidence that the FDA would have rejected the Gaetas' proposed hepatotoxicity warning two years later.

Nor does Perrigo suggest that it supplied the FDA with any "evaluation or analysis concerning the specific dangers" posed by such concomitant use, and that the FDA refused to act. *See Levine*, 129 S. Ct. at 1199. Rather, both in 2002 and 2006, the only evidence before the FDA consisted of what was submitted with the citizen petition *in favor of* including ibuprofen as a safe drug as well as what the FDA itself had reviewed or solicited from the industry and the public. *See* 71 Fed. Reg. 77314, 77316-17, 77328-29; 67 Fed. Reg. 54139, 54140-41. In this context, Perrigo's insistence that the FDA *considered* and *rejected* hepatotoxic warnings associated with

ibuprofen is—just like in *Levine*—nothing more than "creative[ ] paraphras[ing]" of the FDA's regulations that "conflat[es] warnings" about the risk of hepatotoxicity associated with acetaminophen and that associated with ibuprofen "to suggest greater agency attention to the question."[10] *See* 129 S. Ct. at 1199 n.6.

[14] Because the evidence presented by Perrigo in this case is no more compelling than the evidence considered and rejected by the Supreme Court in *Levine*, 129 S. Ct. at 1198-99, we conclude that Perrigo did not meet its burden of demonstrating by clear evidence that the FDA would have rejected the Gaetas' proposed label change.

3. There is no obstruction of purpose.

Even if compliance with state and federal law is not "impossible," state claims may still be preempted if they " 'stand[ ] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.' " *Hillsborough Cnty.*, 471 U.S. at 713 (citation omitted). In this case, Perrigo asserts that exposing generic manufacturers to liability for inadequate warnings would either force them out of the market or require them to raise prices to offset potential liability costs, thereby thwarting the goal of the Hatch-Waxman Amendments to deliver low cost generic drugs to consumers. Perrigo also argues that requiring generic manufacturers to place warnings on their products that do not appear on the

[10]Perrigo also asserts that the FDA later "required the liver warning plaintiffs seek on prescription-strength ibuprofen but not on OTC ibuprofen," which it argues implies that the FDA was aware of potential risks but made a calculated decision to include the warning only on prescription drugs. Perrigo, however, fails to provide any support for this assertion. In any event, as the Gaetas argue, the conclusion to be drawn from this is quite the opposite: the fact that the FDA later required these liver warnings on prescription-strength ibuprofen suggests that the FDA might also have accepted similar warnings for the OTC ibuprofen had Perrigo or any other manufacturer suggested such warnings.

corresponding brand name products would lead to loss of consumer confidence in generic drugs, which consumers already regard as being less safe and effective than the brand name drugs.

[15] As to Perrigo's first argument, there is no indication that when Congress passed the Hatch-Waxman Amendments it intended the goal of delivering low cost generic drugs to supplant the FDCA's overall goal of providing consumers with safe and effective drugs. As both the Fifth and Eighth Circuits have recognized, the Hatch-Waxman Amendments must be considered as "part and parcel" of the FDCA, and not as a separate statutory framework. *See Demahy*, 593 F.3d at 448; *Mensing*, 588 F.3d at 612. We join those two circuits in concluding that while the Hatch-Waxman Amendments were meant to provide an inexpensive and easy way for generic drugs to enter the market, they were not intended as a relief from the fundamental requirement of the FDCA that all marketed drugs remain safe.

Indeed, in enlarging the FDA's powers to protect the public health and to assure the safety and effectiveness of drugs, "Congress took care to preserve state law." *Levine*, 129 S. Ct. at 1195-96. "Evidently, [Congress] determined that widely available state rights of action provided appropriate relief for injured consumers."[11] *Id.* at 1199; *see also Mensing*, 588 F.3d at 603 ("[W]e decline to assume that Congress intended to shield from tort liability the manufacturers of the majority of the prescription drugs consumed in this country and leave

[11]As the Supreme Court observed, had Congress considered state-law suits to be an obstacle to its objectives, "it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history." *Levine*, 129 S. Ct. at 1200. But despite its 1976 enactment of an express preemption provision for medical devices, Congress has not enacted such a provision for the remainder of the FDCA. *Id.*; *see also Riegel*, 552 U.S. at 327 ("Congress could have applied the pre-emption clause to the entire FDCA. It did not do so, but instead wrote a pre-emption clause that applies only to medical devices.").

injured parties like Mensing no legal remedy." (citing *Foster*, 29 F.3d at 170)). "If Congress had intended to deprive injured parties of a long available form of compensation"—and to do so in such an inconsistent manner—"it surely would have expressed that intent more clearly." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) (citation omitted).

Perrigo's argument that consumers will lose confidence in generic drugs if they contain warnings different from those of the brand name drugs also fails. First, it is purely speculative that consumers will opt for a more expensive brand name product—or against purchasing any product at all—if the less expensive generic product contains additional warnings. Second, as previously noted, there is no indication Congress intended consumers to have access to low cost drugs at the expense of safety. Finally, by using the "prior approval" process, a generic manufacturer can avoid consumer confusion because, if the FDA accepts the proposed change, that change would be imposed uniformly on both generic and brand name manufacturers. *See* 57 Fed. Reg. 17950, 17961.

IV

[16] The state law duty to warn by an appropriate label on the generic ibuprofen drug was not preempted by federal law. Compliance with both state and federal law was not "impossible." Additional warnings would not stand as an obstacle to the accomplishment of purposes and objectives of Congress. Perrigo failed to present clear evidence that the FDA would have rejected the specific hepatotoxicity warnings proposed by the Gaetas. Accordingly, we **REVERSE** the district court's summary judgment in favor of Perrigo on the ground of federal preemption.

REVERSED and **REMANDED**.