

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF KENTUCKY
LEXINGTON

PHILIP C. WEISS, et al.,)	
)	
Plaintiffs,)	
)	Civil Action No. 5:05-527-JMH
v.)	
)	
FUJISAWA PHARMACEUTICAL)	MEMORANDUM OPINION AND ORDER
CO., et al.,)	
)	
Defendants.)	

** ** ** ** **

This matter is before the Court on Defendant Novartis Pharmaceutical Corporation's ("NPC") motion to dismiss on federal preemption grounds [Record No. 84]. Upon sufficient consideration, this Court finds that Plaintiffs have sufficiently set forth a failure-to-warn claim that is not preempted by the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 et seq, or by Food and Drug Administration (FDA) regulations.

I. BACKGROUND

A. Factual Background

On or about August 2003, Plaintiff Philip C. Weiss began using Elidel and Protopic to treat atopic dermatitis.¹ Weiss subsequently developed cancer, lymphadenopathy, lymphomas, serious

¹ Elidel is the trade name under which NPC markets the drug pimecrolimus. Protopic is the trade name under which Fujisawa Healthcare markets the drug tacrolimus. Elidel and Protopic are topical calcineurin inhibitors, drugs prescribed to treat atopic dermatitis. Atopic dermatitis, commonly known as eczema, is a non-life-threatening skin condition that causes an itchy rash and dry, scaly skin. NPC filed the motion to dismiss, so this opinion only addresses the failure-to-warn claims regarding Elidel.

respiratory diseases and other injuries. Plaintiffs allege that these conditions were substantially caused by Weiss' use of Elidel and Protopic. Plaintiffs also allege that Defendant NPC "had knowledge that Elidel, since at least as early as the year 1999 posed serious adverse health risks of cancer and lymphomas to patients who would use and apply Elidel for the treatment of skin diseases to which the product was designed to treat" and that NPC failed to warn Weiss or his physician, Dr. Joseph Bark, of these health risks. (Second Amended Complaint ¶ 95). Plaintiffs accordingly raised failure-to-warn claims under theories of strict liability and negligence. (Second Amended Complaint Counts VII and X). Defendant NPC has moved to dismiss these claims under the theory that they are preempted by FDA regulations.

B. FDA Regulations

The regulations regarding drug labeling were substantially revised in 2006. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006). However, this case involves drugs that were approved and prescribed to the plaintiff prior to FDA's adoption of the new regulations, so the relevant question is whether the pre-2006 approval process preempts state law failure-to-warn claims.²

² If the new regulations preempt state failure-to-warn claims whereas the old regulations did not, this creates an issue of retroactivity. If a rule represents a change in prior position, it "typically will not apply retroactively in the absence of an express statutory authorization of retroactive rulemaking." *Orr v.*

The FDCA, codified as 21 U.S.C. §§ 301 et seq. (1938), requires that the FDA approve all prescription drugs as "safe and effective" prior to sale in the United States. 21 U.S.C. § 355(a). To obtain approval for a new drug, a manufacturer must submit to the FDA a portfolio of information, including "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." *Id.* § 355(b)(1)(A). The manufacturer must also submit proposed labeling to be included when the drug is distributed. *Id.* § 355(b)(1)(F).

After a drug has been approved, manufacturers must still update product labeling when new information becomes available. "The labeling shall be revised 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) (2003). A manufacturer must generally seek FDA approval before it makes any changes to the FDA-approved label and packaging. *Id.* § 314.70(b). However, manufacturers may "add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the

Hawk, 156 F.3d 651, 653 (6th Cir. 1998). However, FDA asserts that the old and new regulations both preempt state law, 71 Fed. Reg. at 3934, so the only issue is what level of deference, if any, this Court should give to FDA's interpretation of its regulations.

product" without prior approval. *Id.* § 314.70(c)(2)(i), (iii). If such a change is made, "[t]he applicant shall promptly revise all promotional labeling and drug advertising to make it consistent with any change in the labeling." *Id.* § 314.70(c). Finally, the FDCA considers a drug misbranded "[i]f its labeling is false or misleading in any particular." 21 U.S.C. § 352(a).

Restrictions on drug labeling do not prohibit manufacturers from disseminating evidence of danger by other means. The comments attached to prior regulations make clear that

[t]hese labeling requirements do not prohibit a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters directed to health care professionals (e.g., "Dear Doctor" letters containing such information) is not prohibited by these regulations.

44 Fed. Reg. 37434, 37447 (June 26, 1979). FDA's regulations indicate that such communication is occasionally expected. "Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care." 21 C.F.R. § 200.5. "[S]ignificant hazard[s] to health" are one example of the "important information" contemplated by this regulation. See 21 C.F.R. § 200.5(c)(1).

C. Regulatory History

On December 13, 2001, the FDA approved NPC's application to market Elidel for the treatment of atopic dermatitis. NPC's application sought FDA approval to market Elidel for short-term or intermittent long-term use in non-immunocompromised patients at least two years of age. As part of the approval process, the FDA evaluated and approved the labeling that NPC submitted. The labeling noted no increase among human clinical subjects in the incidence of lymphoma or other cancers but did report an increase in lymphoma in animals given high doses of the drug. As a result of these animal studies, which were consistent with the clinical data for tacrolimus, FDA required NPC to conduct ongoing studies to monitor the incidence of malignancies related to long-term use of Elidel.

In October, 2003, FDA's Pediatric Advisory Subcommittee to the Anti-Infective Drugs Advisory Committee met to discuss cancer rates among pediatric patients treated with calcineurin inhibitors for atopic dermatitis. FDA scientists recognized at the meeting that lymphoma is associated with systemic exposure to a calcineurin inhibitor through oral treatment with the drug. Because calcineurin inhibitors are absorbed through the skin, topical use of the drugs may cause low-level systemic exposure. After assessing animal studies, clinical trials, and post-marketing information about calcineurin inhibitors, committee members recognized that the long latency period for malignancies; the low

incidence of those diseases, particularly in children; and the lack of any centralized registry or reporting system for many forms of malignancies, all contributed to the difficulty in determining whether topical use of calcineurin inhibitors increases the risk for cancer. While numerous individual participants recommended the adoption of particular strategies to manage the potential risk for malignancies, the subcommittee did not make any formal decision or recommendation on the issue of labeling, which was not the topic on which the meeting had been convened.

On February 15, 2005, the Pediatric Advisory Committee again met to discuss the potential cancer risk in children from the use of topical immunosuppressants and methods of risk management. In calling the committee meeting, FDA was particularly concerned about off-label use of the drugs in infants.³ Prior animal studies had raised a concern that "chronic, intermittent exposure . . . could lead to an increased incidence of Hodgkin and Non-Hodgkin lymphoma as well as melanoma and non-melanoma skin cancers." FDA Feb. 7, 2005 Briefing Memo at 2-3. In the meantime, FDA had at least one

³ "Off-label use" refers to prescriptions of drugs for indications that are not described on the drug's approved label. Although drug manufacturers are forbidden from specifically encouraging off-label use, it is apparently common in many clinical areas. In this particular case, the Briefing Memorandum for the committee meeting explained that, although neither Elidel nor Protopic was approved or recommended for use in children under age 2, approximately 500,000 prescriptions for the drugs had been dispensed for children in that age range between June 2003 and May 2004.

new animal study and additional malignancy and other adverse event reports for Elidel and Protopic, all raising concerns regarding the connection between calcineurin inhibitors and an increased risk of cancer. FDA's Office of Pediatric Therapies and Division of Pediatric Drug Development both recommended to the Pediatric Advisory Committee that the labels for Elidel and Protopic be modified to reflect a potential risk of cancer, particularly in young children treated with the drugs.

At the February 15 meeting, the Pediatric Advisory Committee voted to recommend a change in labeling for Elidel and Protopic to alert medical professionals of a potential association between calcineurin inhibitors and lymphoma and other malignancies. Specifically, the committee recommended a boxed warning recognizing the "potential increased risk of cancer in humans, based on animal studies," while noting that "there is inadequate human data at this time to ascertain the cancer risk from the topical use of calcineurin inhibitors." On March 10, 2005, FDA issued a public health advisory to inform doctors and patients about potential cancer risk from the use of Elidel and Protopic. On January 19, 2006, FDA approved revised labeling for Elidel containing a boxed warning that "rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Elidel Cream" and recommending that "continuing long-term use of topical calcineurin

inhibitors . . . in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis." See Letter to Judge Dalzell at 4-8, *Perry v. Novartis Pharmaceuticals Corp.*, No. 05-5350 (E.D. Pa. Sept. 21, 2006).

D. FDA's Position

According to FDA, its "long-standing" view has been that FDA approval of labeling preempts conflicting or contrary state law. 71 Fed. Reg. at 3934. This is only true in that the FDA has taken this position since around 2001. In 1979, FDA declared, "It is not the intent of the FDA to influence civil tort liability of the manufacturer." 44 Fed. Reg. at 37447. In 1988: "FDA regulations establish minimal standards necessary, but were not intended to preclude states from imposing additional labeling requirements." 63 Fed. Reg. 66378-01, 66384 (Dec. 1, 1988). Most recently, in the proposed drug labeling rule published in December 2000 - the preliminary version of the final rule promulgated in January, 2006 - the agency stated, "[T]his proposed rule does not preempt State law." 65 Fed. Reg. 81082, 81103 (2000). In 2001, FDA began asserting its current preemption position in *amicus* briefs filed in state products liability lawsuits. It ultimately included this position in the preamble to the final labeling rule issued on January 24, 2006.

1. *Preamble to the 2006 Regulation*

"FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law." 71 Fed. Reg. at 3934. This position "represents the government's long standing views on preemption, with a particular emphasis on how that doctrine applies to State laws that would require labeling that conflicts with or is contrary to FDA-approved labeling." *Id.* "State law actions . . . threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs." *Id.* at 3935.

2. *FDA Letter to Judge Dalzell*

Another products liability lawsuit based on Elidel is pending against NPC in the United States District Court for the Eastern District of Pennsylvania. *Perry* (E.D. Pa. filed Oct. 12, 2005). At the request of Hon. Judge Stewart Dalzell, FDA submitted a brief specifically addressing their position on preemption as applied to Elidel. Generally, it is the FDA's position that "state tort law is preempted if it imposes liability for a company's failure to provide a warning that FDA has rejected, or would reject, as scientifically unsubstantiated, or for a company's conduct in providing a warning that FDA deems necessary for the safe and efficacious use of a prescription drug." Letter to Judge Dalzell at 2, *Perry* (E.D. Pa. Sept. 21, 2006). FDA's specific position on Elidel is,

[I]t is not possible at this stage of the litigation for FDA to determine whether the plaintiffs' failure-to-warn claim is preempted in its entirety, because the plaintiffs have not yet articulated with specificity the warning that they assert should have been provided. That said, FDA has concluded that certain types of failure-to-warn claims that could be advanced in this proceeding are preempted. A claim that the defendants should have warned that Elidel causes lymphoma would be barred under the doctrine of federal conflict preemption, because it conflicts with FDA's determination, as of January 2006, that causation has not yet been established. Similarly, a claim based on the defendants' failure to warn of risks that were not included on the approved label for Elidel would be preempted absent scientific evidence in support of such a claim.

Id. (emphasis in original).

II. STANDARD OF REVIEW

NPC claims that state law failure-to-warn claims are preempted by FDA regulations under the doctrine of conflict preemption. Conflict preemption occurs "when compliance with both state and federal law is impossible, or when the state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objective of Congress.'" *United States v. Locke*, 529 U.S. 89, 109 (2000). Preemption is not limited to the acts of Congress, for an administrative agency acting within the boundaries of its authority may displace state law. *United States v. Shimer*, 367 U.S. 374, 383 (1961). Unless preemption is the "clear and manifest purpose of Congress," courts begin with the presumption that state law is not superseded. *Wisconsin Pub. Intervenor v. Mortier*, 501 U.S. 597, 605 (1991).

Since this is a motion to dismiss, under Rule 12(b)(6), this Court must also construe the complaint in the light most favorable to the plaintiff and accept as true all well-pleaded factual allegations. *Cooper v. Parrish*, 203 F.3d 937, 944 (6th Cir. 2000).

III. DEFERENCE TO FDA

There are three types of deference this Court could apply to the FDA's position. See *Chevron U.S.A. v. Natural Res. Def. Council*, 467 U.S. 837 (1984) (holding that, when agency is construing a statute formulated by adjudication or rulemaking, court should only ask if agency's position is founded on a "permissible" construction of the statute if statute is otherwise silent); *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (holding that, when agency is interpreting its own regulation, interpretation is "controlling unless plainly erroneous or inconsistent with the regulation"); *Skidmore v. Swift*, 323 U.S. 134, 140 (1944) (holding that other interpretations are "entitled to respect" but only to the extent that opinion has the "power to persuade"). Because of the inconsistency in the FDA's position, this Court finds that both are entitled only to the most limited level of deference. They "are 'entitled to respect' . . . but only to the extent that those interpretations have the 'power to persuade.'" *Christensen v. Harris County*, 529 U.S. 576, 587 (2000) (citing *Skidmore v. Swift*, 323 U.S. 134, 140 (1944)).

As an initial matter, neither the preamble nor the letter to Judge Dalzell are entitled to *Chevron* deference. Under *Chevron*, agency interpretations of the statutes they administer receive great deference. However, "[i]nterpretations such as those in opinion letters - like interpretations contained in policy statements, agency manuals, and enforcement guidelines, all of which lack the force of law - do not warrant *Chevron*-style deference." *Christensen*, 529 U.S. at 587. Even though it represents FDA's formal position on a matter and obligates the agency to follow it until amended or revoked, 21 C.F.R. § 10.85(g), an advisory opinion is also entitled only to limited deference because it is not subject to notice and comment procedures. See *Orr*, 156 F.3d at 655 ("[A]lthough the rule has the force and effect of a published regulation, it is not the product of a notice and comment rulemaking process, and is therefore akin to an internal rule entitled to only limited deference."). Advisory opinions include "[a]ny portion of a Federal Register notice other than the text of a proposed or final regulation, e.g., a notice to manufacturers or a preamble to a proposed or final regulation." 21 C.F.R. § 10.85(d)(1).

Though the preamble and the letter to Judge Dalzell are not entitled to *Chevron* deference, they would still ordinarily be entitled to *Auer* deference. An agency's interpretation of its own regulation is "controlling unless plainly erroneous or inconsistent

with the regulation." *Auer*, 519 U.S. at 461 (1997) (internal quotations omitted). Under this standard, "we must defer to the [agency's] interpretation unless an 'alternative reading is compelled by the regulation's plain language or by other indications of the [agency's] intent at the time of the regulation's promulgation.'" *Thomas Jefferson University v. Shalala*, 512 U.S. 504, 512 (1994) (quoting *Gardebring v. Jenkins*, 485 U.S. 415, 430 (1988)).

FDA's assessment of the preemptive effect of its own regulations would therefore generally be entitled to considerable deference. However, the Supreme Court has also held that "the consistency of an agency's position is a factor in assessing the weight that position is due." *Good Samaritan Hosp. v. Shalala*, 508 U.S. 402, 417 (1993); see also *INS v. Cardoza-Fonseca*, 480 U.S. 421, 448 n. 30 (1987) ("An agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is 'entitled to considerably less deference than a consistently held agency view'") (quoting *Watt v. Alaska*, 451 U.S. 259, 273 (1981)).

FDA's position has not been consistent and is therefore entitled only to *Skidmore* deference. "The weight of such a judgment in a particular case will depend upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those

factors which give it power to persuade." *Skidmore*, 323 U.S. at 140.

IV. ANALYSIS

With these factors in mind, this Court finds that the approach taken by the District Court for the Eastern District of Pennsylvania is persuasive:

Thus, to the degree that the FDA seeks to address ambiguities in the FDCA or in its own regulations, we will give that opinion great weight. Where, however, the agency attempts to "supply, on Congress's behalf, the clear legislative statement of intent required to overcome the presumption against preemption," no deference is warranted. *Desiano v. Warner-Lambert & Co.*, --- F.3d ---, 2006 WL 2846454, at *11 fn. 9 (2d Cir. Oct. 5, 2006). "Agencies may play the sorcerer's apprentice but not the sorcerer himself." *Alexander v. Sandoval*, 532 U.S. 275, 291 (2001).

Memorandum at 8, *Perry*. In particular, FDA's position is persuasive insofar as it rejects failure-to-warn claims (1) based on conduct that allegedly occurred prior to and during the labeling approval process and (2) based on proposed warnings that FDA has specifically considered and rejected as scientifically unsubstantiated.

A. Fraud on the FDA

The Sixth Circuit's line of cases addressing federal preemption of fraud-on-the-FDA and similar claims is also instructive. These cases demonstrate that, even in the absence of the FDA's opinion, the Sixth Circuit would likely find that

failure-to-warn claims based on conduct that occurred prior to and during the labeling approval process would be preempted.

In *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), the Supreme Court held that "fraud-on-the-FDA" claims are preempted by the Medical Devices Amendment ("MDA") to the FDCA. The Supreme Court dispensed with the presumption against preemption because "the relationship between a federal agency and the entity it regulates is inherently federal in character." *Id.* at 347. Since "[s]tate-law fraud-on-the-FDA claims inevitably conflict with the FDA's responsibility to police fraud consistently with the Agency's judgment and objectives," *Id.* at 350, and since "fraud-on-the-FDA claims would also cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Agency, will later be judged insufficient in state court," *Id.* at 351, the Supreme Court held that state-law fraud-on-the-FDA claims were preempted.

Buckman, standing alone, does not apply to this case because (1) the relevant claims are failure-to-warn, not fraud-on-the-FDA, and (2) prescription drugs are not covered by the MDA. However, subsequent Sixth Circuit cases extended *Buckman's* logic into both areas.

In *Garcia v. Wyeth-Ayerst Laboratories*, 385 F.3d 961, 965-66 (6th Cir. 2004), the Sixth Circuit found that the a prescription drug fraud-on-the-FDA claim was preempted.

In *Kemp v. Medtronic, Inc.*, 231 F.3d 216 (6th Cir. 2000), the Sixth Circuit held that at least some failure-to-warn claims are preempted under the same logic set forth in *Buckman*. The court recognized that failure-to-warn encompasses at least two types of claims:

[A failure-to-warn claim] could be read as asserting that the warnings found in the label and literature approved by the FDA for the Model 4004 and Model 4004M were inadequate under Ohio law . . . The statement in Count IV could also be read, however, to assert a wholly separate and distinct claim that defendant acquired information subsequent to the FDA approval of the Model 4004M and before implantation of the device that would lead a reasonable manufacturer to warn patients and the medical community.

Kemp, 231 F.3d at 236-37. "[T]o the extent that plaintiffs' claim is premised on the adequacy of the warnings reviewed and approved by the FDA, our analysis of the 'fraud on the FDA' claim applies equally to the failure to warn claim, and the claim is similarly preempted." *Id.*⁴ Based on these cases, prescription drug failure-to-warn claims "premiered on the adequacy of the warnings approved and reviewed by the FDA" would be preempted.

B. FDA Regulations

⁴ The Sixth Circuit would later revisit the issue whether failure-to-warn claims based on information obtained after approval were also preempted in *Cupek v. Medtronic, Inc.*, 405 F.3d 421 (6th Cir. 2005). While the court ultimately found that these claims were preempted, it did so under the procedures specifically enacted in the Medical Devices Amendment. *Id.* This distinction is important because Congress explicitly included a preemption provision in the MDA. 21 U.S.C. § 360k(a).

FDA's regulations are also instructive insofar as they provide several avenues by which a drug manufacturer may warn patients and healthcare providers should they discover new evidence of a particular risk following the approval of the original label. The manufacturer can add or strengthen a warning without FDA approval so long as the warning does not render the label misleading. 21 C.F.R. § 314.70(c)(2), 21 U.S.C. § 352(a). If the manufacturer obtains new evidence regarding a risk the FDA previously found unsubstantiated, the manufacturer may still inform the FDA and seek approval for a new label. 21 C.F.R. § 314.70(b). Finally, the regulations encourage drug manufacturers to periodically send important information, including information regarding risks, to healthcare providers. *Id.* § 200.5. Therefore, there are a number of ways a drug company can warn users of its product's risks other than the original FDA-approved label.

In this case, a state law requirement to provide an additional warning would not conflict with federal regulations. At the time Elidel was prescribed for Philip Weiss, the FDA had not made a conclusive finding regarding a link between the use of topical calcineurin inhibitors and increased cancer risk. In addition, NPC could conceivably have possessed information not available to the FDA that they could have communicated to the FDA, to healthcare providers, or to patients, consistent with FDA regulations. Finally, state law failure-to-warn claims would not disrupt the

FDA's regulatory scheme because FDA's regulations specifically provide avenues by which pharmaceutical companies may strengthen warnings following approval of the original label.

V. CONCLUSION

For the foregoing reasons, **IT IS ORDERED** that NPC's motion to dismiss on federal preemption grounds [Record No. 84] be, and the same hereby is, **DENIED**.

This the 28th day of November, 2006.



Signed By:

Joseph M. Hood *JMH*

United States District Judge