IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

ANDREA PERRY, et al.	:	CIVIL ACTION
v.	:	
NOVARTIS PHARMA. CORP., et al.	:	NO. 05-5350

MEMORANDUM

Dalzell, J. October 16, 2006

This case arises from Andreas Perry's diagnosis of lymphoblastic lymphoma three years ago. Andreas' parents, plaintiffs in this action, allege that Andreas's use of Elidel[1], a prescription drug for the treatment of atopic dermatitis[2], caused his lymphoma. Plaintiffs raise a number of claims against the makers of Elidel, including fraud, breach of warranty, and negligent failure to warn.

Defendants have moved to dismiss the failure to warn claims on the basis that the federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., and the Food and Drug Administration regulations promulgated under that statute, impliedly preempt all such claims. Although we find that some failure to warn claims, particularly those where the FDA has made a specific determination regarding the danger, are indeed preempted, that preemption is not so broad as to foreclose the possibility that the Perrys can make out a claim for negligence

[1] Elidel is the trade name under which Novartis markets the drug pimecrolimus.

[2] Atopic dermatitis, also known as eczema, is a skin condition causing an itchy rash and dry, scaly skin. It is particularly common in infants and young children.

consistent with the pleadings before us. Accordingly, defendants' motion must be denied.

Factual Background

On December 13, 2001, the FDA approved Novartis's[3] application to market Elidel for the treatment of atopic dermatitis. Novartis'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 product labeling that Novartis submitted. That labeling noted no increase among the 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 a similar drug, tacrolimus,[4] the FDA required Novartis to conduct ongoing studies to monitor the incidence of malignancies related to long-term use of Elidel.

In October, 2003, the FDA's Pediatric Advisory Subcommittee to the Anti-Infective Drugs Advisory Committee met to discuss cancer rates among pediatric patients treated with

[3] Plaintiffs have sued four separate corporate entities: Novartis Pharmaceuticals Corporation, Novartis Corporation, Novartis Pharma GmbH, and Novartis AG. The first three entities are controlled, directly or indirectly, by Novartis AG. Because, for the purposes of this motion, the distinctions among the entities are not material, we will simply refer to all four defendants as Novartis.

[4] Fujisawa Healthcare markets tacrolimus under the trade name Protopic. The FDA approved tacrolimus on September 8, 1999 for use in treating atopic dermatitis.

calcineurin inhibitors.[5] Although some members expressed concerns -- in particular that the labels for topical calcineurin inhibitors should be modified to specifically warn against their use in patients under the age of two -- the Committee that month made no recommendation to the FDA on the question of pediatric use of calcineurin inhibitors.

On February 15, 2005, the Committee again met to discuss calcineurin inhibitors. In particular, reports of off-label use[6] of the drugs in children under two caused concern among the members of the Committee. At its February 15 meeting, the Committee voted to recommend a so-called "Black Box" warning about the possible increased risk of malignancies associated with the topical use of calcineurin inhibitors, and the lack of long-term safety data on the use of the drugs. On March 10, 2005, the FDA issued a public health advisory warning doctors and patients about the possible cancer risk. On January 19, 2006, the FDA approved modified labeling for Elidel including the "Black Box" warning.

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[5] Both pimecrolimus and tacrolimus belong to a class of drugs known as calcineurin inhibitors, so called because they reduce immune activity by inhibiting the activity of the enzyme calcineurin. Prior to the approval of Elidel and Protopic, calcineurin inhibitors were used as systemic immunosuppressants in organ transplant patients. Systemic use of calcineurin inhibitors has long been known to increase cancer risk and the drugs used in organ transplant patients are labeled accordingly. Because pimecrolimus and tacrolimus are applied topically, it was not known at the time of approval whether long-term use of those drugs posed the same risk.

[6] "Off-label use" refers to those 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, in many clinical areas it is, apparently, quite common.

On or about April 30, 2003, just after Andreas Perry's second birthday, his parents sought treatment for his eczema. The Perrys' pediatrician gave them samples of Elidel, which they used to treat Andreas. Six months later, in October, 2003, Andreas was diagnosed with lymphoblastic lymphoma.

Jurisdiction and Legal Standard

We have jurisdiction under 28 U.S.C. § 1332(a), as the plaintiffs are all citizens of Pennsylvania and the defendants are, variously, citizens of Delaware, New Jersey, New York, Germany, and Switzerland. Plaintiffs' second amended complaint added claims against two non-diverse defendants, Jae A. Sparks and Mary Gianstasio. In our Order of October 5, 2006, we dismissed without prejudice the claims against Sparks and Gianstasio under Fed. R. Civ. P. 21. Because complete diversity exists between the plaintiffs and the remaining defendants, and the amount in controversy exceeds $75,000, we have jurisdiction over the subject matter.

We may grant defendants' motion to dismiss only if, having taken all allegations in the complaint as true, "it is clear that no relief could be granted under any set of facts that could be proved consistent with the allegations." Doe v. Delie, 257 F.3d 309, 313 (3d Cir. 2001).

Review of the FDCA and FDA Regulations

Because Novartis contends that plaintiffs' claims are

preempted by the FDCA and the corresponding FDA regulations,[7] we first review the statute and those regulations in some detail.

The FDCA requires that the FDA approve any drug before it is sold in interstate commerce. 21 U.S.C. § 355(a). In order to obtain approval for a new drug, a manufacturer[8] 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). In addition, the manufacturer must provide the agency with proposed labeling to be included with the drug when it is distributed. Id. § 355(b)(1)(F).

Manufacturers must update product labeling when new information becomes available. In particular, "[t]he 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).

In general, once the drug and its labeling are approved, a manufacturer must seek FDA approval before making any changes to its label and packaging. Id. § 314.70(b). Some

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[7] The regulations regarding labeling of drugs were substantially revised in 2006. See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006). Because the relevant claims in this case deal with Novartis's alleged failure to provide adequate warnings in 2003, we examine the regulations as they existed then.

[8] Although we refer to manufacturers here, the regulations apply equally to companies that market, distribute and/or repackage drugs that an outside entity manufactures for them.

changes are permissible without prior approval, so long as the manufacturer notifies the FDA when the change is made. In particular, the regulations allow changes to labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction," id. § 314.70(c)(2)(i), or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product," id. § 314.70(c)(2)(iii).[9] If any such 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."[10] Id. § 314.70(c). "This particular regulation was promulgated precisely to allow drug-makers to quickly strengthen label warnings when evidence of new side effects are [sic] discovered." Witczak v. Pfizer, Inc., 377 F. Supp. 2d 726, 729 (D. Minn. 2005).

The FDCA also directly limits changes to a drug's labeling, stating that any "false or misleading" statement in the labeling will render the drug misbranded, making distribution of the drug unlawful. See 21 U.S.C. 352(a).

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[9] Some have claimed that this provision is rarely invoked, see, e.g., Richard M. Cooper, Drug Labeling and Products Liability: The Role of the Food and Drug Administration, 41 Food Drug Cosm. L.J. 233, 236 (1986), but as will become clear shortly, what matters in the preemption analysis is not whether, in practice, manufacturers perceive a potential conflict between federal and state law, but whether there is an actual and direct conflict. Thus, in the preemption analysis, what matters is whether Novartis could have, consistent with federal law, added a warning to its labeling materials.

[10] In this context, "labeling" refers to the package insert, which is primarily directed at prescribing physicians. This is the reason for the distinction between "labeling" and "promotional labeling."

Any restrictions that the FDA may place on drug labeling do not prohibit manufacturers from disseminating evidence of a danger by other means. When it originally promulgated these regulations, the agency made clear that:

> These 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). Indeed, the FDA has promulgated particular regulations guiding the dissemination of information to health care professionals, see 21 C.F.R. § 200.5, making it clear that it expects such communication to take place.

Deference to FDA

Because the FDA has, at our request, filed an amicus brief in this case, before moving on to the preemption analysis itself, we must determine the degree of deference to afford the FDA's statements regarding the preemptive effect of its regulations. Certainly, under Chevron U.S.A. v. Natural Res. Def. Council, 467 U.S. 837 (1984), agency interpretations of statutes they administer receive great deference. Chevron deference is only warranted, however, when the agency speaks in the exercise of its authority "to make rules carrying the force of law." United States v. Mead Corp., 533 U.S. 218, 226-227

(2001). Thus, to the degree that FDA regulations construe the FDCA, we should defer to the agency's construction. Further, if FDA regulations are ambiguous, agency statements resolving those ambiguities are worthy of our deference. See Christensen v. Harris County, 529 U.S. 576, 588 (2000). In the absence of "power to control," which would entitle it to deference under Chevron, however, the FDA's construction of its regulations is entitled to respect only inasmuch as it has the "power to persuade." Mead, 533 U.S. at 228 (quoting Skidmore v. Swift & Co., 323 U.S. 134, 140 (1944)). To be sure, because of its expertise in the area, the FDA's construction of its own regulations is likely to carry great weight. But where an interpretation has changed frequently in significant respects, the persuasive force of the argument diminishes.

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).

The Preamble

Much has been made, both in the briefs for this case and in opinions in recent similar cases, about the effect of the

Preamble to the new labeling rules issued on January 24, 2006. In the Preamble, the FDA stakes out a strong position on the preemptive effect of its labeling requirements. See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. at 3933-36. For a number of reasons, we find that the Preamble need not affect our analysis of the issues in this case.

As a preliminary matter, the Preamble is not a binding portion of the regulations, but is instead an advisory opinion. See 21 C.F.R. § 10.85(d)(1) (identifying as an advisory opinion "[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"). While an advisory opinion "obligates the agency to follow it until it is amended or revoked," it can be changed at any time and a change does not require notice and comment. Id. § 10.85(e),(g).

It is by no means clear what effect an advisory opinion issued in 2006 could have on the obligations to which Novartis was subject in 2003. If, as the FDA contends in the Preamble, the statement represents merely an application of "existing preemption principles," 71 Fed. Reg. at 3934, then it produces no change in Novartis's rights or obligations and should not affect our analysis. If, on the other hand, the Preamble represents a change of policy, whether or not it has the force of law, we cannot apply it to this case. The FDA cannot retroactively absolve Novartis of a duty it may have owed the Perrys in 2003.

Finally, and most importantly, the Preamble deals chiefly with "specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated." Id. Although the Preamble does not purport to limit the situations in which state law causes of action are preempted, it lists six types of claims that, at a minimum, the agency believes should be preempted. The category most relevant to this case is "claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn." Id. at 3936 (emphasis added). Here, it is undisputed that no such proposal had been made to the FDA in 2003.

For all of these reasons, the Preamble is not entitled to any special consideration in our analysis.

Preemption Analysis

"[F]ederal pre-emption of state law can occur in three types of situations: where Congress explicitly pre-empts state law, where pre-emption is implied because Congress has occupied the entire field and where pre-emption is implied because there is an actual conflict between federal and state law." Pokorny v. Ford Motor Co., 902 F.2d 1116, 1120 (3d Cir. 1990) (citing Schneidewind v. ANR Pipeline Co., 485 U.S. 293 (1988)). The parties agree that this case presents a question of implied preemption based on an actual conflict between federal and state law.

A court will find an actual conflict "when it is impossible to comply with both state and federal law, or where the state law stands as an obstacle to the accomplishment of the full purposes and objectives of Congress." Id. (quoting Schneidewind, 485 U.S. at 299-300). Such a conclusion is not to be found lightly. "Consideration under the Supremacy Clause starts with the basic assumption that Congress did not intend to displace state law." Maryland v. Louisiana, 451 U.S. 725, 746 (1981). On the record presented here, the bar to a finding of preemption is raised even higher because the FDCA provides no remedy for an injured consumer. Thus, a finding of preemption here will foreclose a remedy that was traditionally available and for which federal law provides no substitute. Courts have (understandably) been particularly reluctant to find preemption in such cases without an unambiguous signal of Congressional intent. See Medtronic, Inc. v. Lohr, 518 U.S. 470, 487 (1996) (plurality opinion) ("It is, to say the least, 'difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.'") (quoting Silkwood v. Kerr-McGee Corp., 464 U.S. 238, 251 (1984)); Bates v. Dow Agrosciences LLC, 544 U.S. 431, 449 (2005) ("If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly.").

Courts should therefore not reach to find that FDA regulations preempt state law claims. There are, to be sure, situations in which preemption of state law claims is necessary

to preserve the structure of the FDA regulatory scheme. The FDCA grants the FDA authority that it must use "to achieve a somewhat delicate balance of statutory objectives." Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 348 (2001). Because the agency is concerned not solely with maximizing safety, but also with balancing a need for safety with a desire to encourage the widespread use of effective treatments, a specific determination by the FDA that a warning is not warranted is dispositive.[11]

Preemption is unwarranted in the absence of clear evidence that state law requiring an additional warning would either compel the manufacturer to violate the terms of the FDCA or the FDA regulations, or would somehow be disruptive of the statutory and regulatory scheme. This would generally limit preemption to cases where the FDA has made a particular determination regarding a proposed warning. The FDA advocates for a somewhat broader scope of preemption. The agency contends that "[a] court must ask whether the warning sought by the plaintiff would have rendered the drug misbranded in the agency's judgment at the relevant time, or if any new warnings proposed to be added to the warning label would have been rejected by the agency as unsubstantiated." FDA Amicus Br. at 11. We think this overstates the scope of preemption. Because the FDA must

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[11] It should be obvious that this can only be true if the FDA scientists who made the specific determination had available to them all of the relevant data. If, for whatever reason, the manufacturer knew of additional data not available to the FDA linking the drug to a safety risk, the dispositive force of the agency's determination would be called into question. Because, in the case of Elidel, the FDA did not make a specific determination during the relevant time regarding the risk of pediatric cancers, we need not address that possibility here.

initiate an enforcement action in order to find a drug misbranded, see Witczak, 377 F. Supp. 2d at 730 ("[T]he FDA has no authority to declare, ipse dixit, that a label is false and misleading. Rather, the government must initiate an enforcement action to establish that the drug is in fact misbranded.") (citing 21 U.S.C. §§ 331-37, 352), it will often not be possible for a court to determine after the fact whether a particular warning would have resulted in such a finding.

We believe it is more in keeping with the narrow scope of preemption to allow state law to require the addition of warnings so long as there has been no specific FDA determination as to the sufficiency of the scientific evidence to support a particular warning. Under the regulations applicable to this case, upon making a change to the labeling the manufacturer is required to submit "a full explanation of the basis for the change" to the FDA. 21 C.F.R. 314.70(c) (2003). This allows the agency to make a prompt determination of the scientific validity of the new warning. The new regulations contain a similar requirement. 21 C.F.R. 314.70(c)(6)(iii) (2006). These provisions allow a manufacturer to obtain a prompt determination from the FDA regarding the sufficiency of the link between the drug and the reported problem. Indeed, "manufacturers typically consult with FDA prior to adding risk information to labeling." 71 Fed. Reg. at 3934. We find, therefore, that state law may require a manufacturer to at least seek FDA approval for the addition of a new warning where there has been no determination by the agency whether there is a link between the adverse health

effect to be warned against and the use of the drug.[12] Where, however, the FDA has made a conclusive determination, positive or negative, as to the existence of a link between the drug at issue and some adverse health consequence, state law cannot mandate that a manufacturer include additional warnings beyond those that the FDA has determined to be appropriate to the risk.

That was the case, for example, in Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514 (E.D. Pa. 2006). In that case, as here, plaintiff advanced a claim based on the defendant drug manufacturers' failure to provide adequate warnings of a known danger, specifically the link between use of Selective Serotonin Reuptake Inhibitors (SSRI's) and increased risk of suicide in adult patients. In Colacicco, however, the FDA had "specifically and repeatedly rejected claims that adult use of SSRI's was associated with increased suicidality." Id. at 527. Over a period of twelve years, in response to citizen complaints and internal findings, agency scientists repeatedly concluded that there was no credible evidence to support a link between SSRI use and increased suicidality in adults and that "the evidence was not strong enough to justify the suggestion of even the possibility of a causal linkage in the labeling." Brief of

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[12] It is an interesting question whether a manufacturer who has sought FDA approval for an additional warning could be held liable for a failure to warn during the pendency of that agency review. We think that state law cannot require a manufacturer to bear the risk of an adverse finding in an FDA enforcement action. Thus, although state law can require a manufacturer to seek FDA approval for a new warning, it cannot require the addition of the warning without approval if there is a reasonable risk that the addition would lead to an FDA determination of misbranding.

United States of America at 9, Colacicco, 432 F. Supp. 2d 514 (No. 05-5500). Thus, in its amicus brief in Colacicco, the FDA argued that including a warning of that risk would render the drug misbranded. Id. at 14-15. Because this made it "impossible to comply with both state and federal law," Pokorny, 902 F.2d at 1120, a finding of preemption was warranted.[13]

It is worth noting that, even where FDA regulations or other federal law prevent a manufacturer from modifying the approved labeling, a modification of the label is not the only form that a warning could take. If, for example, a plaintiff claimed that a manufacturer was negligent in not sending a letter to prescribing physicians or other health care professionals, that might present a different case, even if modification of the approved labeling were prohibited. Because plaintiffs are not specific in the complaint as to the nature of the warning that Novartis should have provided,[14] even if we were to find that Novartis could not have modified the FDA-approved labeling of Elidel to include a warning about pediatric cancers, we would still be obliged to deny defendants' motion if a warning of some

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[13] Judge Baylson in Colacicco also found preemption on the grounds that Apotex, as the manufacturer of a generic drug, was not permitted to modify the labeling to reflect new warnings. See 21 U.S.C. § 355(j)(2)(A)(v) (prohibiting manufacturers of generic drugs from modifying the label approved for the branded drug). Again, given that plaintiff claimed that he was entitled to a warning, the fact that such a warning would have been a violation of federal law was sufficient for a finding of preemption.

[14] This is, of course, not a defect in the complaint since Fed. R. Civ. P. 8(a) does not require at this stage that a plaintiff state precisely what form the warning should have taken.

other type would have been permissible under the regulations. The FDA has made clear that warnings other than labeling changes, such as letters to health care professionals, are permissible and the labeling regulations do not bar them.[15] See 44 Fed. Reg. 37434, 37447 (quoted supra).

In this case, a state law requirement to provide an additional warning would not force Novartis to choose between violating state and federal law. At the time Elidel was prescribed for Andreas Perry, the FDA had made no finding regarding a link between use of topical calcineurin inhibitors and increased cancer risk in children[16] and no statute or regulation prevented Novartis from adding the warning. Because federal law was effectively silent on whether such a warning was warranted, state law was not barred from requiring it.

Even where compliance with both federal and state law is possible, preemption may be found where the existence of state

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[15] We do not mean to suggest that letters to health care professionals are beyond the scope of regulations. As with all other communications from manufacturers, such statements must not be "false and misleading" or they will render the drug misbranded. They need not, however, meet the specific approval requirements of 21 C.F.R. Part 201.

[16] It appears from the materials before us that the October, 2003 meeting of the Pediatric Advisory Subcommittee was inconclusive and generated no recommendation to the FDA. It would seem, therefore, that this represents a middle ground between the Committee's subsequent determination to require a warning and the situation in Colacicco where the Committee specifically found that the evidence did not support a warning. This middle ground allows a manufacturer that is in possession of information not considered by FDA scientists, or one who desires to act in an abundance of caution, to take steps to include an additional warning pending the FDA's more conclusive determination. In any case, the meeting took place in October, 2003, well after Andreas Perry began taking Elidel.

law tort suits would disrupt the statutory and regulatory scheme that Congress envisioned. Thus, in Buckman, the Court found that the FDA was "amply empower[ed]" to police the submissions of medical device manufacturers and that allowing individuals to bring state law "fraud-on-the-FDA" claims would skew the balance of statutory objectives that the FDA sought to preserve. 531 U.S. at 348.

Requiring Novartis to add a warning to the Elidel label would not disturb the balance of the regulatory scheme since FDA regulations make specific accommodation for adding a warning in the situation the Perrys allege. Indeed, given the recent concerns about the effectiveness of the FDA's safety monitoring of recently approved drugs, see, e.g., Gardiner Harris, Study Condemns F.D.A.'s Handling of Drug Safety, N.Y. Times, Sept. 23, 2006, at A1, the availability of state law tort suits provides an important backstop to the federal regulatory scheme.

If, at some future date, Congress determines that FDA monitoring is sufficiently effective on its own to warrant the elimination of state law incentives for manufacturers to provide adequate warnings, it also has the authority to declare that failure to warn suits, like the Perrys' action, are preempted. Until it does so, however, in the absence of a specific FDA safety determination, such suits can go forward.

Accordingly, we will deny Novartis's motion to dismiss.

BY THE COURT:

/s/ Stewart Dalzell, J.

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ORDER

AND NOW, this 16th day of October, 2006, upon consideration of defendants' motion to dismiss on federal preemption grounds (docket entry # 58), plaintiffs' memorandum in opposition (docket entry # 67), the brief of the Pennsylvania Trial Lawyers Association as amicus curiae (docket entry # 72), the materials filed by the Food and Drug Administration as amicus curiae (docket entry # 75) and the parties' filings of supplemental authority (docket entries 70, 74, 77, and 80) and for the reasons articulated in the accompanying Memorandum of Law, it is hereby ORDERED that:

1. Defendants' motion to dismiss is DENIED; and

2. Defendants shall ANSWER plaintiffs' second amended complaint by October 30, 2006.

BY THE COURT:

/s/ Stewart Dalzell, J.