UNITED STATES DISTRICT COURT
DISTRICT OF NEW HAMPSHIRE

Karen L. Bartlett
and Gregory S. Bartlett

v.

Civil No. 08-cv-358-JL
Opinion No. 2009 DNH 144

Mutual Pharmaceutical
Company, Inc. *et al.*

O R D E R

This case presents a question currently pending before three different federal courts of appeal: whether state-law tort claims alleging the defective labeling of generic drugs are pre-empted by federal law. See Morris v. Wyeth, Inc., No. 09-5509 (6th Cir. Apr. 27, 2009); Demahy v. Wyeth, Inc., No. 08-31204 (5th Cir. Dec. 16, 2008); Mensing v. Wyeth, Inc., No. 08-3850 (8th Cir. Dec. 10, 2008). The defendants, Mutual Pharmaceutical Company, Inc. and United Research Laboratories, Inc., move for judgment on the pleadings, see Fed. R. Civ. P. 12(c), on claims by the plaintiffs, Karen L. and Gregory S. Bartlett, alleging that Karen suffered serious injuries from Sulindac, a generic drug manufactured by the defendants. The defendants argue that all of the plaintiffs' state-law causes of action are pre-empted by Title I of the Drug Price Competition and Patent Term

Restoration Act of 1984,[1] part of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA").[2] This court has subject-matter jurisdiction under 28 U.S.C. § 1332(a)(1) (diversity).

After considering the parties' extensive briefing and oral argument, the court denies the defendants' motion for judgment on the pleadings. The Bartletts' claims do not present an obstacle to the accomplishment and execution of the full purposes and objectives of Congress in the Hatch-Waxman Amendments, nor does complying with the state law underlying those claims make it impossible to comply with the Hatch-Waxman Amendments or any other federal law identified by the defendants. The Supreme Court's recent decision on the pre-emptive effect of federal drug regulation on state tort law in Wyeth v. Levine, 129 S. Ct. 1187 (2009), makes that result clear. Accordingly, the Bartletts' claims are not pre-empted.

I. Applicable legal standard

Federal "preemption is an affirmative defense on which [the] defendant bears the burden of proof." Cambridge Literary Props.,

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[1]Pub. L. 98-417, tit. I, 98 Stat. 1985, codified as amended at 21 U.S.C. § 355(j) (1999 & supp. 2009).

[2]Ch. 675, 52 Stat. 1040 (1938), codified as amended at 21 U.S.C. §§ 301 et seq. (1999 & supp. 2009).

Ltd. v. W. Goebel Porzellanfabrik G.m.b.H. & Co. KG, 510 F.3d 77, 102 (1st Cir. 2007), cert. denied, 129 S. Ct. 58 (2008); see also Wyeth, 129 S. Ct. at 1193 (characterizing a manufacturer's argument that federal drug law pre-empted the plaintiff's claims as a defense). While an affirmative defense can support a Rule 12(c) motion for judgment on the pleadings, it can do so "only where it is (1) definitively ascertainable from the complaint and other sources of information that are reviewable at [the pleadings] stage, and (2) [these] facts establish the affirmative defense with certitude." Citibank Global Mkts., Inc. v. Rodriguez Santana, 573 F.3d 17, 23 (1st Cir. 2009).

II. Background

A. The Bartletts' allegations

For purposes of the defendants' motion for judgment on the pleadings, the court accepts the following allegations of the Bartletts' complaint as true. See Gray v. Evercore Restructuring L.L.C., 544 F.3d 320, 324 (1st Cir. 2008). In December 2004, Karen Bartlett's physician prescribed her Sulindac, a non-steroidal anti-inflammatory drug manufactured by the defendants, for pain in her right shoulder. Within weeks of filling the prescription, she went to a local emergency room complaining of "pimple like bumps, spots or blisters on her face, a fever, eye irritation," and other symptoms. She was soon diagnosed with

Stevens-Johnson syndrome progressing to toxic epidermal necrolysis, a serious and potentially fatal condition characterized by large areas of lesions on and necrosis of the skin and mucous membranes. See Dorland's Illustrated Medical Dictionary 1872 (31st ed. 2007). She spent approximately three months in the hospital recovering, including two months in a medically induced coma, and emerged with permanent injuries.

Sulindac is the generic version of a drug originally approved by the FDA in 1978; the generic version at issue here was approved in 1991. The Bartletts allege that, following this approval, the defendants "had an ongoing duty to conduct postmarketing safety surveillance for any reports of serious adverse events associated with Sulindac including any such report in the medical literature" and that, had they done so, they would have uncovered information compelling them "to warn physicians about the dangers" of the drug, including associations with Stevens-Johnson syndrome and toxic epidermal necrolysis.

The Bartletts' complaint asserts seven counts:

- strict product liability--failure to warn (count 1);
- strict product liability--defective in design or manufacture (count 2);
- fraud, in the sense that the defendants "made misrepresentations of material facts . . . and omitted and/or concealed material facts" about the risks of Sulindac (count 3);

- breach of implied warranty that Sulindac was "of merchantable quality and safe and fit for [its intended] use" (count 4);

- breach of express warranty that Sulindac "was safe and well accepted by patients and was safe for long-term use" (count 5);

- negligence in failing "to use reasonable care in designing, testing, labeling, marketing, supplying, distribution [*sic*] and selling" Sulindac (count 6);

- gross negligence based on the same omissions (count 7).

B. The statutory and regulatory scheme

1. Overview of the FDA approval process

The FDCA prohibits the "introduction into interstate commerce [of] any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug."[3] 21 U.S.C. § 355(a). As discussed in detail below, those two subsections provide two different procedures for obtaining the requisite approval from the Secretary of Health and Human Services to distribute a new drug. The Secretary oversees the Food and Drug Agency in carrying out these procedures. See id. § 393(b)(2)(A).

[3]The FDCA defines "new drug," in relevant part, as "[a]ny drug . . . the composition of which is such that such drug is not generally recognized among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(p)(1).

Subsection (b) authorizes a new drug application ("NDA") containing certain specified data, e.g., "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 for use," "a full list of the articles used as components of such drug," and "specimens of the labeling proposed to be used for such drug." Id. § 355(b)(1). The Secretary shall approve such an application absent specified grounds for denial. See id. § 355(c)(1)(A). These grounds include, e.g., that the required investigations "do not include adequate tests . . . to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," that "results of such tests show that such drug is unsafe for use under such conditions," and that "based on a fair evaluation of all material facts, such labeling is unsafe or misleading in any particular." Id. § 355(d).

Subsection (j), the Hatch-Waxman Amendments, sets forth a process under which "[a]ny person may file with the Secretary [of HHS] an abbreviated application for the approval of a new drug." Id. § 355(j)(1) (emphasis added). Rather than the data required of a full-blown NDA by subsection (b), an abbreviated application ("ANDA") must show that "the conditions of use prescribed, recommended, or suggested in the labeling have been previously approved for . . . a listed drug," id. §§ 355(j)(2)(A)(i)

(internal quotation marks and parentheses omitted), and that each of a number of specified characteristics of the new drug is "the same as that of the listed drug." Id. §§ 355(j)(2)(A)(ii)-(v). These characteristics include the drug's active ingredient, route of administration, dosage form, strength, and labeling. See id. A "listed drug" is a "drug which has been approved for safety and effectiveness under subsection (c) of this section," id. § 355(j)(7)(A)(i)(I), which, as just discussed, governs the approval of applications submitted under subsection (b). The Secretary must approve an ANDA absent certain specified grounds, e.g., "information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug," id. § 355(j)(4)(B), or "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug,"[4] id. § 355(j)(4)(G).

The Hatch-Waxman Amendments, then, authorize the approval of a new drug without demanding the information that would otherwise be required in an application under subsection (b), i.e., the reports of safety and effectiveness investigations and the like,

[4]There is an exception to this requirement "for changes required because of differences approved under a petition filed under [21 U.S.C. § 355(j)(2)(C)] or because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). That exception is not at issue in this case.

provided the same drug has been previously approved for the same conditions under that more rigorous process. As one committee report on the Amendments noted, their "focus . . . is to provide the Food and Drug Administration with sufficient information to assure that the generic drug is the same as the listed drug that has previously been determined to be safe and effective." H.R. Rep. No. 98-857, pt. 1, at 21 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2654 (footnote and parenthetical omitted). The term "generic drug," in this context, refers to a "listed drug" not covered by a patent, whether because that patent has expired or otherwise. See 21 U.S.C. § 355(j)(2)(A)(vii).

2. ANDA procedures before Hatch-Waxman

As this committee report also noted, the FDA had, at that point, already been approving ANDAs for generic drugs, but only insofar as such a drug was "the same as [a] pioneer [i.e., non-generic] drug" approved prior to 1962. H.R. Rep. No. 98-857, pt. 1, at 16, 1984 U.S.C.C.A.N. at 2649; see also Abbreviated New Drug Applications, 48 Fed. Reg. 2751, 2755 (Jan. 21, 1983) (later codified at 21 C.F.R. § 314.2 (1984)). This temporal limitation had its origins in the Drug Amendments of 1962, which "required that all drugs, both generic and pioneer, . . . be approved as safe and effective [by the FDA] prior to marketing"; before those amendments, the FDA had approved drugs on the basis of safety

alone. H.R. Rep. No. 98-857, pt. 1, at 16, 1984 U.S.C.C.A.N. at 2649; see also Drug Amendments of 1962 §§ 102(d) (codified as amended at 21 U.S.C. § 355(d)).

To carry out the mandate of the Drug Amendments, the FDA "created the drug efficacy study (DESI) to determine if all pre-1962 [approved] drugs were effective." H.R. Rep. No. 98-857, pt. 1, at 16, 1984 U.S.C.C.A.N. 2647, 2649. The FDA later concluded that the reports generated in that study, together with other available data, "constituted a body of information sufficient, in the case of most DESI drugs determined to be effective, to conclude that the same drug product produced by another manufacturer would also be safe and effective if properly manufactured and used under the same conditions." Abbreviated Drug Applications, 43 Fed. Reg. 39126, 39127 (proposed Sept. 1, 1978). Thus, the FDA promulgated a rule allowing an ANDA for a particular new drug upon a finding that such an approach was "sufficient." Abbreviated Applications, 35 Fed. Reg. 6574, 6575 (Apr. 24, 1970) (later codified at 21 C.F.R. § 130.4 (1971)). This rule required, in relevant part, that an ANDA contain "[l]abeling that is in accord with the labeling conditions described in the finding." Id. (later codified at 21 C.F.R. § 130.4(f)(2) (1971)).

After receiving ANDAs for new drugs varying from ones approved through the DESI program in ways that "pose[d]

significant questions of safety or effectiveness," however, the FDA proposed a new rule limiting the ANDA process. 43 Fed. Reg. at 39127. This rule, promulgated in 1983, permitted an ANDA only upon a finding that a drug product "covered by [DESI] may be approved for marketing without the submission of additional evidence of preclinical and clinical studies to show safety and effectiveness." 48 Fed. Reg. at 2755 (parenthetical omitted) (later codified at 21 C.F.R. § 314.2(a) (1984)).

The new rule also provided that such a finding, i.e., "that an [ANDA] is suitable for a drug product[,] applies only to a product that is the same in active ingredient, dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding." Id. (later codified at 21 C.F.R. § 314.2(b)(2)). This amendment did not alter the requirement that an ANDA contain "[l]abeling that is in accord with the labeling conditions described in the finding that an [ANDA] is sufficient." Id. at 2756 (later codified at 21 C.F.R. § 314.2(f)(2)).

At the time it proposed this rule, the FDA announced its "inten[t] to extend the ANDA concept at a later time to post-1962 drug products by publishing criteria for making a determination about these drugs," noting that the rationale for the ANDA concept covered drugs approved before 1962 only--since only they had been subjected to the rigors of the DESI process. 43 Fed.

Reg. at 39128. The FDA never did act on its own to make the ANDA process available for drugs approved after 1962, H.R. Rep. No. 98-857, pt. 1, at 16, 1984 U.S.C.C.A.N. at 2649, so Congress acted through the Hatch-Waxman Amendments, "generally extend[ing] the procedures used to approve generic copies of pre-62 drugs to post-62 drugs," id., at 14, 1984 U.S.C.C.A.N. at 2647.

Doing so, the committee report recognized, would allow the FDA to approve such drugs without requiring human clinical trials, "retesting" which the FDA saw as "unnecessary and wasteful"--as well as "unethical"--"because the drug has already been determined to be safe and effective." Id. at 16, 1984 U.S.C.C.A.N. at 2649. The committee report also noted that the "approximately 150 drugs approved after 1962 that [were] off patent and for which there [was] no generic equivalent" at that time "could be approved in generic form if there was [an ANDA] procedure," resulting in significant cost savings. Id. at 17, 1984 U.S.S.C.A.N. at 2650.

3. ANDA procedures after Hatch-Waxman

The FDA later proposed amending its regulations to implement the ANDA procedure set forth in the Hatch-Waxman Amendments. See Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872 (proposed July 10, 1989). In relevant part, the FDA proposed "to add a new requirement with respect to the submission of labeling

as part of an ANDA" to effect Hatch-Waxman's rule that an ANDA "show that the proposed labeling for its drug product is the same as that of the reference listed drug." Id. at 28884 (emphasis added). The FDA then promulgated rules specifying that an ANDA must include "[a] statement that the applicant's proposed labeling is the same as the labeling of the reference listed drug except for" enumerated differences not relevant here. Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17985-86 (Apr. 28, 1992) (later codified at 21 C.F.R. §§ 314.94(a)(8)(iii)-(iv) (1993)).

These rules also stated that the FDA would deny an ANDA if it was "insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug," id. at 17992 (later codified at 21 C.F.R. § 314.127(a)(7) (1993)), and that the FDA "may" begin proceedings to withdraw its approval of an ANDA if it found "[t]hat the labeling for the drug product that is the subject of the [ANDA] is no longer consistent with that for the listed drug," id. at 17993-94 (later codified at 21 C.F.R. § 314.150(b)(10) (1993)) (emphasis added), both with exceptions not relevant here.[5]

[5]Though the FDA has since made slight modifications to § 314.94, see Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66378-01, 66397 (Dec. 1, 1998), these are in relevant part the same regulations that were in effect at the time Karen Bartlett was prescribed and ingested Sulindac, and that remain in effect today. See 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7), 314.150(b)(10) (2008).

During the notice-and-comment period on these rules, the FDA received feedback that "the labeling provisions should be revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information." Id. at 17961. The FDA noted that it "disagree[d] . . . . [T]he ANDA's product labeling must be the same as the listed drug's product labeling because the listed drug product is the basis for ANDA approval." Id. But the FDA also noted that

> Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

Id. (emphasis added).

Further, in response to a comment that "FDA should create a mechanism to compel ANDA holders to revise their labeling to conform to the listed drug product once the ANDA is approved," the FDA observed that 21 U.S.C. § 355(e)(2)

> authorizes the withdrawal of approval of an application if 'there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or

> suggested in the labeling thereof.' This provision applies to both ANDA and NDA drug products. Because an ANDA must have labeling that is the same as the reference listed drug under [21 U.S.C. § 355(j)(2)(A)(v)], FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling. FDA, therefore, has revised § 314.150 to permit the agency to withdraw approval of the ANDA if the applicant fails to maintain labeling in compliance with the requirements of the Act.

Id. at 17968(emphases added). In explaining this revision, the FDA noted its agreement with comments that it "should create a new provision authorizing the agency to withdraw an [ANDA] if the [ANDA] holder failed to modify its labeling to match labeling changes in the reference listed drug."[6] Id. at 17970. Thus, the FDA explained, "§ 314.150(b)(10) states that the ANDA applicant's failure to maintain drug labeling that is consistent with that of the listed drug may be grounds for withdrawing approval of the [ANDA]." Id. (emphasis added).

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[6]The FDA had initially proposed to "retain its current regulations under § 314.150 stating the grounds for the withdrawal of approval of applications and abbreviated applications for drugs under [21 U.S.C. § 355(e)]," while adding regulations "to describe additional circumstances under which the agency will suspend or withdraw ANDA approval under [21 U.S.C.] § 355(j)(5)]." 54 Fed. Reg. at 28904. Section 355(j)(5), in essence, directs the Secretary to withdraw or suspend an ANDA upon the withdrawal or suspension of its listed drug's application; those were the "additional circumstances" described in the added regulations. 54 Fed. Reg. at 17993 (codified at 21 C.F.R. §§ 314.151, 314.153 (2008)).

4. Revisions to drug labeling

Revisions to drug labeling are covered under another FDA regulation, 21 C.F.R. § 314.70, "Supplements and other changes to an approved application." Under this rule, before making "[c]hanges in labeling," id. § 314.70(b)(2)(v)(A), the applicant must submit, and the FDA must approve, a "supplement" describing the change, id. §§ 314.70(a)(1)(i), (b)(1). The rule has exceptions, however, see id. § 314.70(b)(2)(v)(A), one of which is for "[c]hanges in the labeling . . . [t]o add or strengthen a contraindication, warning, precaution, or adverse reaction," id. § 314.70(c)(6)(iii)(A). In such a case, "the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change," rather than waiting for the FDA to approve it. Id. § 314.70(c)(6)(iii). This is known as a "changes being effected" or "CBE" supplement. Id. § 314.70(c)(3). As with other changes in labeling, the FDA may ultimately disapprove a change made through the CBE process, in which case "it may order the manufacturer to cease distribution of the drug product(s) made with the . . . change." Id. § 314.70(c)(7).

This version of the rule was promulgated in 2004, following the passage of Food and Drug Administration Modernization Act of

1997 ("FDAMA").[7] Supplements and Other Changes to an Approved Application, 69 Fed. Reg. 18728, 18764-65 (Apr. 8, 2004).[8] The Modernization Act provided that, "[w]ith respect to a drug for which there is in effect an approved application under section 355 . . . , a change from the manufacturing process approved pursuant to such an application . . . may be made, and the drug as made with the change may be distributed." 21 U.S.C. § 356a(a). The Act authorized the Secretary to "designate a category of . . . changes for the purpose of providing that . . . the holder involved may commence distribution of the drug involved upon the receipt by the Secretary of a supplemental application for the change," rather than wait for approval. Id. § 356a(d)(3)(B)(ii).

So, by opening the CBE process to labeling changes that added or strengthened warnings and the like under 21 C.F.R. § 314.70(c)(6)(iii)(A), the Secretary created "a category of changes" that could be implemented upon receipt of a supplemental application effecting them. In substance, however, a rule like § 314.70(c)(6)(iii)(A) had been in effect since 1965, when the Secretary promulgated a rule that, if a supplemental application

[7]Pub. L. 105-115, § 116(a), 111 Stat. 2296, 2313 (codified at 21 U.S.C. § 356a (1999)).

[8]The rule was subsequently revised in ways not relevant here. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, 71 Fed. Reg. 3922, 3997 (Jan. 24, 2006).

proposed "additional warning, contraindication, side-effect, [or] precaution information" to package labeling, that change "should be placed in effect at the earliest possible time." Supplemental New-Drug Applications. 30 Fed. Reg. 911, 993 (Jan. 30, 1965) (later codified at 21 C.F.R. § 130.9(d)(1) (1965)). To effect this goal, the FDA announced in the rule a policy "to take no action against a drug or applicant solely because changes of [this] kind . . . are placed in effect by the applicant prior to his receipt of a written notice of approval." Id. at 994 (later codified at 21 C.F.R. § 130.9(e)).

Despite some renumbering, see 39 Fed. Reg. 11680, 117123 (Mar. 29, 1974) (recodifying § 130.9 as § 314.8), the relevant substance of this rule remained the same until 1985, when the rule took its current form. See New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7498-99 (Feb. 22, 1985) (later codified at 21 C.F.R. § 314.70 (1985)). Though the Hatch-Waxman Amendments had already become law at that point, the FDA had yet to promulgate the regulations implementing them; when the agency did so, however, the only change it made to the rule on supplemental applications, § 314.70, was to add a paragraph directing that "[t]he applicant shall comply with the patent information requirements under section 505(c)(2) of the act."[9]

[9]When FDA amended the rule again in response to the Modernization Act, its only substantive edit to the CBE

Abbreviated New Drug Applications, 57 Fed. Reg. at 17983 (codified at 21 C.F.R. § 314.70(f)).

But later, in a 2008 proposal to amend 21 C.F.R. § 314.70(c) "to reaffirm that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information," the FDA stated in a footnote that "CBE changes are not available for generic drugs approved under an [ANDA] 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." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848-01, 2849 n.1. (proposed Jan. 16, 2008). The footnote cited 21 C.F.R. § 314.150(b)(10)--which provides, again, that the FDA may attempt to revoke its approval of an ANDA if its labeling is not "consistent with" that of the listed drug--as well as the FDA's comments on ANDA applicants' labels, quoted above.

The FDA did not, however, propose to amend any of its regulations to clarify that an ANDA holder could not avail itself of a CBE supplement. See id. Nor did its final version of the proposed rule contain any such provision. See Supplemental

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provision, § 314.70(c)(6), was to allow distribution of the revised drug product "upon receipt by the agency of the supplement for the change," rather than "promptly" as under the former rule. Compare 69 Fed. at 18764-65 with 50 Fed. Reg. at 7498-99.

Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603-01 (Aug. 22, 2008). And the footnote in the proposal did not acknowledge that, when the FDA promulgated its new rule on ANDA applications following Hatch-Waxman, it included a provision that "[t]he applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications to an approved abbreviated application."[10] 57 Fed. Reg. at 17987 (codified at 21 C.F.R. § 314.97).

5. Generic manufacturers' reporting obligations

The ANDA regulations promulgated after Hatch-Waxman require that "each applicant having an [ANDA] . . . shall comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences." Id. at 17983 (codified as amended at 21 C.F.R. § 314.98(a)). Section 314.80 requires an applicant to report (A) "each adverse drug experience that is both serious and unexpected . . . as soon as possible but in no case later than 15 calendar days of the initial receipt of the information by the applicant," 21 C.F.R. § 314.80(c)(1)(i), and (B) every other "adverse drug experience . . . at quarterly intervals, for 3 years from the date of approval . . . and then

[10]21 C.F.R. § 314.71 sets forth the procedures for submitting a supplement to an application.

at annual intervals," id. § 314.80(c)(2)(i).[11] Furthermore, an applicant "shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA." Id. § 314.80(b).

Congress also addressed the ongoing responsibilities of generic drug manufacturers in the Food and Drug Administration Amendments Act of 2007.[12] This law requires the Secretary to "promptly notify the responsible person"--defined as the holder of an application for a prescription drug approved under subsection (b), see 21 U.S.C. § 355(o)(2)--"or, if the same drug approved under subsection (b) of this section is not currently marketed, the holder of an approved application under subsection (j)," "if the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug." 21 U.S.C. § 355(o)(4). The holder of the ANDA approval must, in response, either "submit a supplement proposing changes to the approved labeling to reflect the new safety information" or explain "why such a change is not warranted." Id. §§ 355(o)(4)(B)(i), (ii).

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[11]Periodic reporting "does not apply to adverse drug experience information obtained from postmarketing studies," 21 C.F.R. § 314.80(c)(2)(iii), nor need such information be included in a "15-day Alert report . . . unless the applicant concludes there is a reasonable possibility that the drug caused the adverse experience," id. § 314.80(e)(1).

[12]Pub. L. 110-85 § 107, 121 Stat. 823, 841.

Paragraph (4) of subsection (o) also contains a "Rule of construction" that it "shall not be construed to affect the responsibility of . . . the holder of the approved application under [21 U.S.C. § 355(j)] to maintain its label in accordance with existing requirements, including subpart B of part 201 and section[] 314.70 . . . of Title 21, Code of Federal Regulations (or any successor regulations)." Id. § 355(o)(4)(I). Subpart B of part 201 imposes labeling requirements on prescription drugs, including that "[t]he labeling shall be revised to include a warning as soon as there is reasonable evidence of a serious hazard with a drug; a causal relationship need not have been proved."[13] 21 C.F.R. § 201.80(e) (2008).

[13]As the result of a 2006 amendment to these rules, "[p]rescription drug products for which a new drug application (NDA), biologics license application (BLA), or efficacy supplement was approved . . . between June 30, 2001 and June 30, 2006," or which was pending or submitted on or after that date, are subject to "Labeling requirements for new and more recently approved prescription drug products" set forth at 21 C.F.R. §§ 201.56(d) and 201.57. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3986-87 (Jan. 24, 2006) (codified at 21 C.F.R. §§ 201.56(b)(1), (d) (2008)). But "[p]rescription drug products not described in paragraph (b)(1) of this section"--i.e., other than for which an NDA, BLA, or efficacy supplement was approved after June 30, 2001--"are subject to the labeling requirements" set forth at 21 C.F.R. §§ 201.56(e) and 201.80. Id. at 3987 (codified at 21 C.F.R. § 201.56(b)(2) (2008)). The version of these rules previously in effect, including when Karen Bartlett was prescribed and ingested Sulindac, contained the same requirement as the 2008 version of § 210.80(e). See Labeling and Prescription Drug Advertising; Content and Format for Labeling for Prescription Human Drugs, 44 Fed. Reg. 37434, 37463 (June 26, 1979) (later codified at 21 C.F.R. § 210.57(e) (1980)). As the FDA explained in enacting the 2008 version of the labeling rules,

II. Analysis

The defendants argue that all of the Bartletts' claims are pre-empted by the Hatch-Waxman Amendments to the FDCA or the ANDA regulations that followed it. "A fundamental tenet of our federalist system is that constitutionally enacted federal law is supreme to state law. See U.S. Const. Art. VI. cl. 2. As a result, federal law sometimes preempts state law either expressly or by implication." N.H. Motor Transp. Ass'n v. Rowe, 448 F.3d 66, 74 (1st Cir. 2006), aff'd, 128 S. Ct. 989 (2008).

The defendants make no express preemption argument here; indeed, nothing in the Hatch-Waxman Amendments expressly preempts state law.[14] Instead, the defendants argue for implicit

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"older drugs not subject to the revised labeling content and format requirements in § 201.57 remain subject to labeling requirements at former § 201.57, which is redesignated as § 201.80." 71 Fed. Reg. at 3965.

[14]As the Bartletts point out, when Congress previously amended the FDCA, in 1962, it included a provision that "[n]othing in the amendments . . . shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. 87-781, § 201, 76 Stat. 780, 793. But this provision, by its terms, applies only to the 1962 amendments (none of which is at issue here) and therefore does not on its face limit the pre-emptive effect--if any--of other provisions of the FDCA, such as the Hatch-Waxman Amendments. Nevertheless, the Supreme Court has viewed this provision as one indicator among many that "Congress took care to preserve state law" while enlarging federal oversight of prescription drugs. Wyeth, 129 S. Ct. at 1195-96 (citing Riegel v. Medtronic, Inc., 128 S. Ct. 999, 1017 (2008) (Ginsburg, J., dissenting)). As discussed infra, that observation does bear upon the pre-emption question here, as it did in Wyeth.

preemption of the Bartletts' state-law claims. "[F]ederal law can preempt state law by implication in two ways," as the court of appeals has explained:

> First, Congress may indicate an intent to occupy an entire field to the exclusion of state law. Second, even if Congress has not occupied the field, state law is nevertheless pre-empted to the extent it actually conflicts with federal law, that is, 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 objectives of Congress.

Good v. Altria Group, Inc., 501 F.3d 29, 47 (1st Cir. 2007) (internal quotation marks and citations omitted), aff'd, 129 S. Ct. 538 (2008). The defendants also make no "field preemption argument," relying solely on "conflict preemption" instead.

The defendants invoke both kinds of conflict pre-emption, though: that complying with the state law underlying the Bartletts' claims (1) would be impossible in light of, and (2) would frustrate the goals of, the Hatch-Waxman Amendments and the subsequent ANDA regulations. Specifically, the defendants argue that, having obtained FDA approval for their generic version of Sulindac under the ANDA procedure envisioned by Hatch-Waxman, they could not change Sulindac's design, or the warnings included in the drug's labeling, without running afoul of federal law (impossibility pre-emption). They further argue that, even if the FDA could approve such a change, it could come only after "substantial expense to obtain the scientific substantiation

necessary to support [it]," frustrating Hatch-Waxman's goal to "increase the availability of low-cost generic drugs" by opening the ANDA process to them (frustration-of-purpose pre-emption).

As the Supreme Court reaffirmed in Wyeth, "'the purpose of Congress is the ultimate touchstone in every pre-emption case.'" 129 S. Ct. at 1194 (quoting Medtronic, Inc. v. Lohr, 518 U.S. 470, 485 (1996) (further internal quotation marks omitted by the Court)). The Court also reaffirmed in Wyeth that "'[i]n all pre-emption cases, and particularly in those in which Congress has legislated . . . in a field which the States have traditionally occupied,' we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'" Id. at 1194-95 (quoting Lohr, 518 U.S. at 485) (further internal quotation marks omitted).

Prior to the Court's decision in Wyeth, the continued validity of this so-called "presumption against pre-emption" had been in some doubt, see, e.g., Rowe, 448 F.3d at 74 n.10; for that reason, perhaps, the parties here have not even mentioned the presumption in their briefing. Wyeth, however, clarified not only that the presumption applies against claims of implied pre-emption, but that it applies in this case, given "the historic presence of state law" in the field of drug labeling. 129 S. Ct. at 1194-95 & n.3; see also id. at 1229 n.14 (Alito, J.,

dissenting) (observing that it "remained an open question--before [Wyeth]--whether [the] presumption applied in conflict pre-emption cases"). Thus, this court must evaluate the defendants' preemption arguments in light of the assumption "that 'Congress does not cavalierly pre-empt state-law causes of action.'" Id. at 1195 n. 3 (quoting Lohr, 518 U.S. at 485). The defendants' arguments do not withstand that level of scrutiny.

A. The plaintiffs' non-failure-to-warn claims

As an initial matter, the court notes that the defendants' arguments are directed almost entirely at the failure-to-warn aspects of the Bartletts' claims. In addition to those claims, however, the Bartletts also allege that the defendants defectively designed or manufactured Sulindac; that they breached their express and implied warranties that Sulindac was safe and fit for its intended use; and that they negligently failed to design or test Sulindac.[15] The defendants suggest, without fully

[15]As discussed supra, the complaint also makes claims for failure to warn, fraud, and breach of implied warranty. Based on the allegations underlying those claims, the court has treated them as dependent, at least in part, on the defendants' alleged failure to warn; similarly, the court has treated the Bartletts' express warranty claim as independent of any statements in Sulindac's labeling. Ultimately, however, the proper characterization of these various claims makes no difference to the outcome of the pending motion, because the court rules that federal law does not pre-empt even those claims that are based on allegedly inadequate warnings.

explaining, that the Hatch-Waxman Amendments still pre-empt these claims because they depend on state law mandating "a generic drug's design to differ from that of the branded on which it is based," which is not permitted under the Hatch-Waxman Amendments.

Assuming, without deciding, that either the letter or spirit of the amendments would prevent the defendants from changing Sulindac's design, that would not conflict with the state law underlying the Bartletts' non-failure-to-warn claims. Those claims allege that the defendants violated state law by distributing a product that was defectively designed or manufactured, that was not fit for its intended use, and without using due care in designing or testing it. While one way to avoid violating state law in this way would be to redesign Sulindac to remove the alleged defect before distributing the drug (or otherwise to meet the standard of care), another way to do so would be to refrain from distributing it at all.[16]

The defendants have not offered an explanation of how state law requiring them to do so would conflict with Hatch-Waxman or

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[16]And a third way to do it would be to distribute the drug only with the allegedly necessary warnings, so, if this were the only theory encompassed by the Bartletts' defective design or manufacture, warranty, and negligence claims, then the defendants' pre-emption arguments would at least be implicated. See Good, 501 F.3d at 36-37 (conducting pre-emption analysis by considering "how [a] particular theory--as opposed to a more generalized claim" set forth as cause of action--implicates federal law). The lack of adequate warnings, however, is not the only omission alleged in support of these claims.

any other federal law.[17] At the outset, then, the defendants' motion must be denied as to the Bartletts' claims for defective design or manufacture, breach of express or implied warranties, and negligence. See Kellogg v. Wyeth, 612 F. Supp. 2d 421, 427-28 (D. Vt. 2008) (ruling that negligence, strict products liability, and express and implied warranty claims were "not exclusively based on failure to add to or strengthen the warnings in FDA-approved labeling for" a generic drug and therefore not pre-empted); Masterson v. Apotex Corp., No. 07-61665, 2008 WL 3262690, at *5 (S.D. Fla. Aug. 7, 2008) ("compliance with a state law duty to warn would conflict with the federal statutory scheme . . . [but] preemption does not extend to manufacturing defect claims that arise separate and apart from [that] claim.")[18].

[17]As the Bartletts point out, the FDA regulations do require that "[a]n applicant who is the sole manufacturer of an approved drug product" give the agency at least six months' notice "prior to discontinuing manufacture," but only for drugs that are "life supporting, life sustaining, or intended for use in the prevention of a serious disease or condition" and "not originally derived from human tissue and replaced by a recombinant product." 21 C.F.R. § 314.81(b)(3)(iii)(*a*) (2008). There is no suggestion that Sulindac fits this narrow category.

[18]Bolin ex rel. Bolin v. SmithKline Beecham Corp., No. 08-60523, 2008 WL 3286973 (S.D. Fla. Aug. 7, 2008) and Valerio ex rel. Valerio v. SmithKline Beecham Corp., No. 08-60522 (S.D. Fla. Aug. 7, 2008) reached the same conclusion; both were decided by the same judge, on the same day, as Masterson.

B. The plaintiffs' failure-to-warn claims

The defendants do argue, at length, that the Hatch-Waxman Amendments and their implementing regulations pre-empt the Bartletts' claims insofar as they arise out of the defendants' alleged failure to warn of Sulindac's potential to cause severe adverse reactions. This argument rests on the premise that, because the FDA approved Sulindac under a process that required the drug's labeling to be "the same as" that of its listed predecessor, they could not have changed the labeling--to add or strengthen a warning about such a reaction, or otherwise--without breaking, or at least standing in the way of, the federal law creating that process, the Hatch-Waxman Amendments.

1. Impossibility pre-emption

To succeed with their impossibility pre-emption argument, the defendants must show "that it would have been impossible for [them] to comply with the state-law duty to modify [Sulindac's] labeling without violating federal law," Wyeth, 129 S. Ct. at 1193, i.e., that "'compliance with both federal and state [law] is a physical impossibility.'" Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta, 458 U.S. 141, 153 (1982) (quoting Fla. Lime & Avocado Growers, Inc. v. Paul, 373 U.S. 132, 142-43 (1963)). As this standard suggests, "[i]mpossibility pre-emption is a demanding

defense," Wyeth, 129 S. Ct. at 1193. The defendants have not satisfied those demands here.

a. The Hatch-Waxman Amendments

Again, the Hatch-Waxman Amendments require that an ANDA contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug," 21 U.S.C. § 355(j)(2)(A)(v), and direct the Secretary to approve an ANDA absent a finding that "information submitted in the application is insufficient" to make such a showing, id. § 355(j)(4)(G), both with exceptions not relevant here. There is no dispute here that, absent these exceptions, Hatch-Waxman thus prevents the approval of an ANDA for a generic drug with labeling that is not "the same as" that of the listed drug; the Bartletts acknowledge as much. But the Bartletts do not seek to hold the defendants liable under state law because they failed to submit an ANDA for their generic Sulindac with labeling that was "the same as" the labeling for the pioneer version.

Rather, as noted in Part II.A, supra, the Bartletts allege that, after securing approval of the ANDA for generic Sulindac with the same labeling as its listed predecessor's, the defendants failed to change the label to warn adequately of the risks of Stevens Johnson-Syndrome and toxic epidermal necrolysis, despite actual or constructive knowledge of these risks. Nothing

in the text of 21 U.S.C. §§ 355(j)(2)(A)(v) or (4)(G), as just quoted, prohibited the defendants from doing so.[19] The defendants point out that, likewise, "there is no provision in the FDCA permitting either a branded or generic manufacturer, following product approval, to change the product's labeling" (emphasis added). But that point is both irrelevant (at least as to the impossibility pre-emption analysis) and incorrect.

Impossibility pre-emption arises where federal and state law "impose directly conflicting duties," e.g., "if the federal law said, 'you must sell insurance,' while the state law said, 'you may not.'" Barnett Bank of Marion County, N.A. v. Nelson, 517 U.S. 25, 31 (1996). To fit their claimed predicament into this framework, the defendants would need to show a federal law saying "You may not change your label" to conflict with the state law underlying the Bartletts' failure-to-warn claims, i.e., "You must change your label." So the defendants' assertion that the FDCA does not say one way or the other whether they can change their label is insufficient.

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[19]For this reason, the defendants are not helped by the FDA's statement in a guidance document that "[a]ll labeling changes for ANDA drug products must be consistent with section 505(j) of the Act." FDA, Guidance for Industry: Changes to an Approved NDA or ANDA 1 (2004), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances24. Section 505(j) as the Act, as just discussed, requires sameness of labeling as a condition of ANDA approval; it does not restrict what happens to the label afterwards.

It is also incorrect, because, as discussed in part II.B.4, supra, the FDAMA allows, "[w]ith respect to a drug for which there is in effect an approved application under section 355 . . . , a change from the manufacturing process approved pursuant to such application." 21 U.S.C. § 356a(a)(1). Both NDAs and ANDAs, of course, are approved under section 355. The FDAMA did restrict such changes: insofar as they qualify as "major manufacturing changes," they must await the Secretary's approval of a supplemental application. Id. § 356a(c)(1). But Congress did not classify labeling changes as "major manufacturing changes" per se, see id. § 356a(c)(2), and, as the CBE regulation demonstrates, neither has the FDA in exercising its authority to further define that term. See 21 C.F.R. § 314.70(c)(6)(iii).

Because 21 U.S.C. § 356a expressly authorizes a manufacturer's changes to an application approved under § 355 of the Act--whether under subsection (b), as in the case of an NDA, or under subsection (j), as in the case of an ANDA--the defendants are incorrect that nothing in the Act permits a manufacturer to change its label post-approval. As another court has noted, while "Congress intended for ANDA applicants to submit identical labeling to the FDA when seeking ANDA approval, the statute is silent as to the manufacturer's obligation after the ANDA is granted." Stacel v. Teva Pharms., USA, 620 F. Supp. 2d 899, 907 (N.D. Ill. 2009) (citation omitted); but see Mensing v.

Wyeth, Inc., 562 F. Supp. 2d 1056, 1064 (D. Minn. 2008) (not discussing FDAMA amendments, and holding that "under the federal statutory scheme, the labeling for generic drugs must always remain the 'same as' that of the name brand drug."), appeal docketed, No. 08-3850 (8th Cir. Dec. 10, 2008); Masterson, 2008 WL 3262690, at *4-*5 (same); Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514, 537-38 (E.D. Pa. 2006) (similar), aff'd on other grounds, 521 F.3d 253 (3d Cir. 2008), vacated, 129 S. Ct. 1578 (2009).[20] Nothing in the "statutory scheme," then, makes it impossible for a manufacturer to change the labeling of an ANDA-approved drug--or to comply with a state-law requirement that it do so.

b. FDA labeling regulations

The analysis of the defendants' impossibility argument does not end there, because "state laws can be pre-empted by federal regulations as well as by federal statutes." Hillsborough County, Fla. v. Automated Med. Labs., Inc., 471 U.S. 707, 713 (1985). At the outset, the court notes that some of the regulations on which the defendants rely, like the provisions of

[20]In Colacicco, the Court of Appeals for the Third Circuit expressly did not decide "whether actions against generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments." 521 F.3d at 271 (footnote omitted).

the Hatch-Waxman Amendments which those regulations implement, do not purport to restrict changes to the label of a generic drug following its approval. See 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7) (quoted in Part II.B.3, supra). Instead, those rules expressly require the generic drug's proposed label to be the same as that of the listed drug, and provide that an ANDA will be denied for failing to demonstrate that. See id.

These regulations, then, do not prevent post-approval changes to the label of an ANDA-approved drug any more than the Hatch-Waxman Act does, as a number of courts have recognized.[21] See Demahy v. Wyeth, Inc., 586 F. Supp. 2d 642, 649-52 (E.D. La. 2008), appeal docketed, No. 08-31204 (5th Cir. Dec. 16, 2008); Laisure-Radke v. Par Pharm., Inc., 2006 WL 901657, at *3-*5 (W.D. Wash. Mar. 29, 2006); Bell v. Lollar, 791 N.E.2d 849, 854 (Ind. Ct. App. 2003); see also Barnhill v. Teva Pharms. USA, Inc., No. 06-282, 2007 U.S. Dist. LEXIS 44718, at *13 (S.D. Ala. Apr. 24, 2007) (reasoning that the comments to the regulations "address labeling requirements necessary for initial approval, not changes to labels for approved ANDA's") (footnote omitted); but see

[21]The same is true of the FDA's remarks in proposing and promulgating these regulations. See Demahy, 586 F. Supp. 2d at 649-52; Barnhill, 2007 U.S. Dist. LEXIS 44718, at *13. As the quotation of one of those remarks in Part II.B.3, supra, illustrates, they refer to the requirement that the applicant propose the same labeling as that of the listed drug; they do not speak to what happens post-approval. See also 57 Fed. Reg. at 17953; 54 Fed. Reg. at 28884.

Morris v. Wyeth, Inc., 582 F. Supp. 2d 861, 868 (W.D. Ky. 2008), appeal docketed, No. 09-5509 (6th Cir. Apr. 27, 2009).[22]

This is not to say that generic drug manufacturers--or any drug manufacturers, for that matter--have carte blanche to make whatever alterations they want to their labels. FDA regulations classify most "labeling changes" as "major changes," see 21 C.F.R. § 314.70(b)(2)(v), meaning that § 356a prohibits a manufacturer from making them without the FDA's prior approval, see 21 U.S.C. § 356a(c)(1). As the Supreme Court observed in Wyeth, "[g]enerally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application." 129 S. Ct. at 1196. But, as Wyeth also noted, the FDA does have a "regulation that permits a manufacturer to make certain changes to its label before receiving the agency's approval"--namely, 21 C.F.R. § 314.70(c)(iii), establishing the "CBE" supplement process. Id. Under this process, as discussed in Part II.B.4, supra, "if a manufacturer is changing a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction,' . . . it may make the labeling change upon filing its

[22]Wilson v. PLIVA, Inc., No. 07-378, 2008 WL 2677049 (W.D. Ky. June 30, 2008), appeal docketed, No. 09-5466 (6th Cir. Apr. 20, 2009), and Smith v. Wyeth, Inc., No. 07-18, 2008 WL 4697002 (W.D. Ky. Oct. 24, 2008), appeal docketed, No. 09-5460 (6th Cir. Apr. 16, 2009), reached the same conclusion as Morris, and were decided by the same court on the same day as that case.

supplemental application with the FDA; it need not wait for FDA approval." Id. (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)).

The Court in Wyeth relied on this regulation in rejecting a manufacturer's argument that state-law failure-to-warn claims were "pre-empted because it is impossible for it to comply with both the state-law duties underlying those claims and its federal labeling duties." Id. at 1196. The Court ruled that, once the risk of the adverse reaction experienced by the plaintiff had become "apparent," triggering a state-law duty to warn of it, "the CBE regulation permitted [the manufacturer] to provide such a warning before receiving the FDA's approval." Id. at 1198. While the Court acknowledged that "the FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application," the Court declined to "conclude that it was impossible for [the manufacturer to comply with both federal and state requirements" without "clear evidence that the FDA would not have approved a change" to effect the warning at issue. Id. The defendants here have not presented any such evidence, i.e., that the FDA would not have approved a change to their labeling to Sulindac to strengthen the warning as allegedly required by state law.

In a supplemental memorandum (Wyeth, again, was decided after the parties here had already fully briefed the motion for judgment on the pleadings), the defendants nevertheless maintain

that the Court's decision does not foreclose their pre-emption defense. They principally argue that, because Sulindac is a generic drug approved through an ANDA, its labeling cannot be changed through the CBE process, which applies only to NDA-approved drugs; therefore, the defendants conclude, it would be impossible for them to comply with both the federal labeling scheme and the state law underlying the Bartletts' failure-to-warn claims.[23] This court rejects with both the premise and the conclusion of that argument.

i. FDA regulations do not forbid adding or strengthening warnings to the labeling of an ANDA-approved drug through the CBE process

***a*. The regulations and their commentary**

Just as nothing in the text of the Hatch-Waxman Amendments forbids a generic manufacturer from changing its drug's label from the listed version's post-approval, nothing in the text of

[23]This argument assumes, of course, that the defendants could not have satisfied their state-law duty to warn by proposing to change Sulindac's label to correct the allegedly inadequate warning, obtaining the FDA's approval of that change, then making it. Cf. Perry v. Novartis Pharm. Corp.. 456 F. Supp. 2d 678, 685 (E.D. Pa. 2006) (ruling that, in the case of a branded drug, "state law may require a manufacturer to at least seek FDA approval for the addition of a new warning" without being pre-empted). The defendants do not expressly argue that, as ANDA holders, they are foreclosed from making a labeling change with the FDA's prior approval, but neither do the Bartletts allege that the defendants would have obtained such approval had they sought it. So the court need not consider this point here.

the CBE regulation forbids a generic manufacturer from using the CBE process to do so. As discussed in Part II.B.4, supra, the CBE regulation represents the FDA's use of its authority, under the FDAMA, to designate labeling changes that add or strengthen warnings and such as "manufacturing changes that are not major manufacturing changes," 21 U.S.C. § 356a(d)(1), and that therefore can be made without prior FDA approval, see id. §§ 356a(d)(1)(B), (3)(B)(ii); the FDAMA, again, does not restrict this process to NDA-approved drugs. The regulation itself also imposes no such restriction: "the holder of an approved application"--not just an approved new drug application under subsection (b)--"may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change." 21 C.F.R. § 314.70(c)(6).

"Determining a regulation's meaning requires application of the same principles that imbue exercises in statutory construction." Morales v. Sociedad Española de Auxilio Mutuo y Beneficencia, 524 F.3d 54, 57 (1st Cir. 2008), cert. denied, 129 S. Ct. 898 (2009). These principles include, first and foremost, "the plain meaning rule, stating that if the language of a . . . regulation has a plain and ordinary meaning, courts need look no further and should apply the regulation as it is written." Textron, Inc. v. Comm'r, 336 F.3d 26, 31 (1st Cir. 2003) (citing, inter alia, Comm'r v. Soliman, 506 U.S. 158, 174 (1993)).

Because, as just discussed, nothing in the text of the CBE regulation declares its process for labeling changes off-limits to ANDA-approved drugs, it would seem "the interpretive odyssey is at an end," Morales, 524 F.3d at 57; like other ANDA holders, the defendants could have availed themselves of the CBE process to add or strengthen the warnings on Sulindac's labeling.[24]

To support their view that the CBE process is nevertheless unavailable to ANDA-approved drugs, the defendants rely on the FDA's remark explaining its revision to § 314.70 following the Hatch-Waxman Amendments. That remark states, in its entirety,

> FDA received no comments on this provision, but has amended the provision to adopt references to statutory, rather than regulatory, provisions to explain what information should be provided. However, the agency wishes to remind ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product

[24]In their opening brief, the defendants claimed that the FDA has permitted CBE supplements seeking to add or strengthen warnings "only where the NDA holder becomes aware of newly discovered safety information" and "there is sufficient evidence of a causal association with the drug." While the publication the defendants purport to quote for this language says nothing of the sort, see Supplemental New-Drug Applications, 30 Fed. Reg. 993 (Jan. 30, 1965), the FDA did amend § 314.70(c)(6)(iii) in 2008--after Karen Bartlett was prescribed and took Sulindac--to limit it to "[c]hanges in the labeling to reflect newly acquired information." 73 Fed. Reg. at 49609. The Court in Wyeth did not "decide whether the 2008 CBE regulation is consistent with the FDCA and the previous version of the regulation," ruling that the manufacturer there "could have revised [the allegedly deficient] label even in accordance with the amended regulation." 129 S. Ct. at 1196. This court can take much the same tack here. The defendants do not argue that they could not have used the CBE supplement process to revise Sulindac's label because they lacked "newly acquired information," but only because the drug was approved on an ANDA instead of a NDA.

> must, with few exceptions, correspond to that for the reference listed drug.

57 Fed. Reg. at 17955. But for the reference to "paragraph 4," this remark might provide some arguable (if atextual) support for the defendants' view: the remark, unlike others they cite, speaks of "the labeling for an ANDA product," rather than the "labeling proposed" for it, and thus might be read to require the labeling to remain the same beyond the approval process.

"Paragraph 4," though, rejects a comment that the FDA "accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label," pointing out that "section 505(j)(2)(A)(v) and (j)(3)(G) of the act requires [*sic*] that the applicant's proposed labeling be the same as that of the listed reference drug" with exceptions not relevant here. Id. at 17953. Those provisions, again, dictate the content of the drug's labeling at the times the ANDA is submitted and approved, not afterwards. In light of the reference to "paragraph 4"--and, in turn, that paragraph's references to 21 U.S.C. § 305(j)--the FDA's comment to § 314.70 cannot be fairly read to extend the mandate that "the labeling proposed for the drug [be] the same as the labeling approved for the listed drug," 21 U.S.C. § 355(j)(4)(G), into the post-proposal, or post-approval, period.

Moreover, the only change the FDA made to the existing version of § 314.70 through the post Hatch-Waxman ANDA

regulations was to add a paragraph requiring the applicant to "comply with the patent information requirements under [21 U.S.C. § 355(c)(2)]." Id. at 17983 (later codified at 21 C.F.R. § 314.70(e) (1993)). It is hard to believe that, in remarking upon this minor revision to the rule, the FDA was in fact expressing the view that the CBE procedures of § 314.70(c)(6)(iii)--which were not being changed, and were not mentioned anywhere in the remark--are off-limits to ANDA-approved drugs.

Indeed, as discussed in Part II.B.4, supra, the FDA had been letting manufacturers make labeling changes to approved drugs that added or strengthened warnings and the like, without prior agency approval, for nearly 20 years prior to Hatch-Waxman, and for more than 27 years prior to the FDA's post-Hatch-Waxman ANDA rules. See 30 Fed. Reg. at 993-94. And, as discussed in Part II.B.2, supra, the FDA had been accepting ANDAs for much of that period. If, in spite of this history, the FDA had intended to place the CBE process for labeling changes off-limits to ANDA-approved drugs in the wake of Hatch-Waxman, the agency might have been expected to do so explicitly by amending § 314.70(c)(6)(iii) to that effect--rather than by making a comment, which might or might not be read that way, while amending the rule in a different way entirely.[25]

[25]By the same reasoning, as well as that set forth in note 21 and the accompanying text, supra, the FDA's remarks in revising its rules on the content and format of drug labeling say

What the FDA actually did was in fact markedly to the contrary: it promulgated 21 C.F.R. § 314.97, entitled "Supplements and other changes to an approved abbreviated application." 57 Fed. Reg. at 17987. The FDA enacted this provision as part of its overhaul of the ANDA rules following Hatch-Waxman, and received--and made--no comments on it. See id. at 17964. This rule, as mentioned in Part II.B.4, supra, provides: "The applicant 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." The "requirements of § 314.70" referred to by § 314.97 include, of course, the CBE provision.

Had the FDA intended that, notwithstanding the clear language of § 314.97, the CBE provision was nevertheless inapplicable to drugs approved via ANDAs, one would have expected

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little if anything about a manufacturer's power to change its labeling after the ANDA is approved. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3929 (Jan. 24, 2006) ("the labeling of a drug product submitted for approval under an ANDA must be the same as the labeling of the listed drug referenced in an ANDA," referring to 21 C.F.R. § 314.94(a)(8)(iv)) (emphasis added), 3963 (making the same statement in explaining that "the requirement to revise the labeling of a reference listed drug in the new format does not have any impact on the duration of exclusivity for the drug and, therefore, does not prevent a manufacturer of a generic product from using the revised labeling of the reference listed drug"). And the defendants point to nothing in the content and format rules themselves affecting a generic manufacturer's ability to add or strengthen a warning post-approval. See 21 C.F.R. §§ 201.56-57.

§ 314.97--or the CBE provision itself--to contain language to that effect or, at least, for the FDA to have clearly explained, in enacting those provisions, that a generic manufacturer could not use the CBE process to change its labels. But the FDA did none of these things. So the defendants are essentially asking this court to rewrite § 314.97 by tacking the words "except for § 314.70(c)(6)(iii)" onto the end.

This court, like almost all of those to have considered the availability of the CBE procedure to ANDA-approved drugs in light of § 314.97, declines to do so. See Stacel, 620 F. Supp. 2d at 907; Kellogg, 612 F. Supp. 2d at 435-36; Demahy, 586 F. Supp. 2d at 649-52; Laisure-Radke, 2006 WL 901657, at *3-*5; accord Foster v. Am. Home Prods. Corp., 29 F.3d 165, 170 (4th Cir. 1994) (citing § 314.97 in recognizing that manufacturers of generic drugs are "permitted to add or strengthen warnings and delete misleading statements on labels, even without prior FDA approval"); but see Morris v. Wyeth, Inc., No. 07-176, 2009 WL 424590, at *6 (W.D. Ky. Feb. 20, 2009);[26] Mensing, 562 F. Supp.

[26]In Morris, the court denied the plaintiff's motion to reconsider its earlier ruling that his state-law failure to warn claims were pre-empted in light of, among other authorities, Demahy. The Morris court's earlier ruling had not taken § 314.97 into account. See 582 F. Supp. 2d 861. On reconsideration, the court discussed

> two possible interpretations of § 314.97. Either the Demahy court is correct that § 314.97 requires ANDA holders to utilize § 314.70, in which case whether or not an ANDA holder can unilaterally change its label is

2d at 1064.[27] Where the language of a regulation is clear, "the courts have no warrant to rewrite [it] in the guise of 'interpretation.'" United States v. Charles George Trucking Co., 823 F.2d 685, 689 (1st Cir. 1987).

> an issue currently pending before the Supreme Court, or the Demahy court is incorrect and § 314.97 merely states that when a brand manufacturer utilizes § 314.70, then so too must the generic manufacturer make that same change to its corresponding drug's label.

2009 WL 424590, at *6 (footnotes omitted).

But the court did not explain the second of these "possible interpretations" in light of either § 314.70 or § 314.97. As to the first interpretation, the court was referring to the Wyeth case, reasoning that "[s]hould the Court determine that brand manufacturers cannot unilaterally change their labels under § 314.70 . . . then neither can generic manufacturers." See id. n.3. In Wyeth, again, the Court held that brand-name manufacturers could unilaterally change their labels under § 314.70(c)(iii)(A). 129 S. Ct. at 1198. Because the contingency essential to the first "possible interpretation" of § 314.97 did not come to pass, and because the second "possible interpretation" was left unexplained, this court declines to follow Morris. The same is true of two other decisions which were issued by the same court on the same day and come to the same conclusion. Wilson v. PLIVA, Inc., No. 07-378, 2009 WL 425027 (W.D. Ky. Feb. 20, 2009); Smith v. Wyeth, Inc., No. 07-18, 2009 WL 425032 (W.D. Ky. Feb. 20, 2009).

[27]In explaining away § 314.97, the court in Mensing relied solely on the FDA's amicus brief to the Third Circuit in Colaccio, which itself stated simply that § 314.97 "does not modify the requirement that the drug label for a generic drug must be the same as the label for the approved innovator drug." 562 F. Supp.2d 1064 (quotation formatting and emphasis omitted). Not only has that brief since been withdrawn, as noted infra Part III.B.1.b.i.*b*, but, in this circuit at least, courts "do not defer to [agency] views espoused only in the context of litigation," including in amicus briefs. Rosenberg v. Merrill Lynch, Pierce, Fenner & Smith, Inc., 170 F.3d 1, 12 (1st Cir. 1999). The court declines to follow Mensing.

That principle is particularly apt in light of what Congress had to say when it recently spoke on the labeling duties of generic drug manufacturers in the Food and Drug Amendments Act of 2007, as discussed in Part II.B.5, supra. Not only does that act require an ANDA holder (provided the drug is no longer marketed by its NDA holder) to submit a supplemental application proposing labeling changes to reflect new safety information identified by the Secretary, or to explain why no change was warranted, 21 U.S.C. §§ 355(o)(4)(B), it also provides that § 355(o)(4) "shall not be construed to affect the responsibility of . . . the holder of the approved application under [21 U.S.C. § 355(j)] to maintain its label in accordance with existing requirements, including subpart B of part 201 and section[] 314.70 . . . of Title 21, Code of Federal Regulations (or any successor regulations)." Id. § 355(o)(4)(I).

As also discussed in Part II.B.5, supra, Title 21, part 201, subpart B of the Code of Federal Regulations requires that "[t]he labeling shall be revised to include a warning as soon as there is reasonable evidence of a serious hazard with a drug," 21 C.F.R. § 201.80(e), at least for prescription drugs not approved on an NDA, BLA, or efficacy supplement after June 30, 2001. See id. § 201.56(b).[28] The surest way to revise a label to include a

[28]Despite the clear language of 21 C.F.R. § 201.56(b)(2) that "[p]rescription drug products not described in paragraph (b)(1) of this section"--i.e., other than for which an NDA, BLA,

warning "as soon as there is reasonable evidence," of course, is to make the revision through the CBE process.

If, as the defendants posit, the portion of § 314.70 which opens the CBE process to labeling changes adding or strengthening warnings does not apply to generic manufacturers--if, in fact, §§ 201.80(e) and 314.70(c)(6)(iii) impose no "responsibility" on ANDA holder "to maintain its label"--then the court is left to wonder, without an explanation, why Congress would have thought it necessary to clarify that 21 U.S.C. § 355(o)(4) does not affect that responsibility. The courts "assume that Congress is aware of existing law when it passes legislation." South Dakota v. Yankton Sioux Tribe, 522 U.S. 329, 351 (1998). Yet the defendants do not attempt to reconcile 21 U.S.C. § 355(o)(4) with their view that neither § 201.80(e) nor § 314.70(c)(6)(iii) applies to them.

In this void, it is reasonable to read the statute as authorizing the FDA to notify an ANDA holder of necessary labeling changes to reflect new safety information, while making clear that an ANDA holder's responsibility to make those changes

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or efficacy supplement was approved after June 30, 2001--"are subject to the labeling requirements" set forth at 21 C.F.R. § 201.80, see note 13, supra, the defendants argue that the rule "does not mean ANDAs are subject to the requirements in § 201.80; it means that any NDA drug first-approved before June 2001 is subject to the regulation." The defendants do not explain, though, how an ANDA-approved drug is anything other than a "[p]rescription drug product[] not described in paragraph (b)(1)." So the court rejects their interpretation.

on its own under 21 C.F.R. § 201.80(e), through the CBE process set forth in 21 C.F.R. § 314.70(c)(6), remains. Indeed, as Wyeth observed of 21 U.S.C. § 355(o)(4), "when Congress granted the FDA this authority, it reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval." 129 S. Ct. at 1198.

The defendants also advance an argument that § 314.70(c)(6) applies only to drugs approved through the NDA process which depends not on § 314.70(c)(6) itself, but on a different provision of the ANDA regulations, 21 C.F.R. § 314.150(b)(10). That regulation, as noted in Part II.B.3, supra, states:

> FDA may notify the applicant, and, if appropriate, all other persons who manufacturer or distribute identical, related, or similar drug products, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or the [ANDA] under [21 U.S.C. § 355(e)] and under the procedure set forth in [21 C.F.R. § 314.200], if the agency finds:
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> . . .
>
> (10) That the labeling for the drug product that is the subject of the [ANDA] is no longer consistent with that for the listed drug referred to in the [ANDA], except for differences approved in the ANDA . . . .

21 C.F.R. § 314.150(b) (emphasis added). The defendants argue that this rule forbade them from using the CBE process to change Sulindac's label, because doing so would have resulted in an

ANDA-approved drug with labeling that was "no longer consistent with that for the listed drug," thus subjecting the ANDA to revocation. The court cannot read § 314.150 that way.

Initially, unlike the admonition repeated throughout the Hatch-Waxman Amendments, and elsewhere in the ANDA regulations, that an ANDA must show "that the labeling proposed for the new drug is the same as the labeling approved for the listed drug," see, e.g., 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added), section 314.150(b)(10) of the regulations requires that the ANDA's labeling be "consistent with that of the listed drug" (emphasis added). While "same" means "being one without addition, change, or continuance," Webster's Third New International Dictionary 2007 (2002), the term "consistent," in contrast, means "showing no significant change, unevenness, or contradiction." Id. at 484.

Where two provisions of the same rule "differ in that one provision uses a term, but the other provision, where it would be equally sensible to use that term if [the agency] desired it to apply," uses a different term instead, "it is generally assumed that [the agency] acts intentionally and purposely in the disparate" wording. United States v. Councilman, 418 F.3d 67, 73-74 (1st Cir. 2005). Here, as one court has noted, "the discrepancy between the manifold use of the phrase 'same as' in the FDA's initial rulemaking on the pre-approval ANDA process is

curious in comparison to the use of the phrase 'consistent with' in the regulation governing post-approval processes," suggesting the terms are not equivalent. Demahy, 586 F. Supp. 2d at 649. Labeling on an ANDA-approved drug that differs from that on the listed version only in having stronger or additional warnings is "consistent with," if not "the same as," that labeling, in that the generic's warning, contraindication, side-effect, and precaution information completely overlaps the brand name's.[29]

Indeed, the FDA enacted § 314.150 in response to a comment that it "should create a new provision authorizing the agency to withdraw an [ANDA] if the [ANDA] holder failed to modify its labeling to match labeling changes in the reference listed drug." 57 Fed. Reg. at 17970. The rule therefore "revised the rule accordingly" to "state[] that the ANDA applicant's failure to maintain drug labeling that is consistent with that of the listed drug may be grounds for withdrawing approval of the [ANDA]." Id. And the FDA also invoked § 314.150 in response to another comment that "FDA should create a mechanism to compel ANDA regulations to

[29]In proposing the regulations, the FDA noted that it would "not accept ANDA's for products with significant changes in labeling," on the theory that those might be necessitated by other kinds of differences from the listed drug that would "jeopardize the safe or effective use of the product." 54 Fed. Reg. at 28885 (emphasis added).

revise their labeling to conform to the listed drug product once the ANDA is approved." Id. at 17968.[30]

As these remarks suggest, then, "the purpose of [the] regulation was not to prevent a generic manufacturer from improving or strengthening its warnings. It was, instead, to ensure that the FDA could require a generic manufacturer to modify its labeling to match labeling changes in the reference listed drug." Barnhill, 2007 U.S. Dist. LEXIS 44718, at *13. So, according to the FDA's own explanation for § 310.150(b)(10), it was not intended to address the opposite situation--where the ANDA holder wants to make labeling changes that have yet to be made on the listed drug.[31]

If anything, the FDA's remarks in promulgating its new ANDA rules after Hatch-Waxman suggest that the agency expected ANDA holders to do just that. In rejecting a comment that it allow "ANDA applicants to deviate from the labeling for the reference listed drug," the FDA noted that, "[a]fter approval of an ANDA,

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[30]To like effect is the FDA's remark, in response to a comment on 21 C.F.R. § 314.127(a)(7), that it had "revised § 314.150 to require ANDA holders to maintain current labeling." 57 Fed. Reg. at 17968.

[31]The remarks do note that § 314.150 "permit[s] the agency to withdraw approval of the ANDA if the applicant fails to maintain labeling in compliance with the requirements of the Act," 57 Fed. Reg. at 17968 (emphasis added), but, as already discussed at length, there is nothing in "the Act" to prevent a generic drug maker from making changes to its labeling post-approval, provided that is done per the applicable procedures. See 21 U.S.C. § 356a.

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." 57 Fed. Reg. at 17961 (emphasis added). While at least one court has taken this statement to "underscore the notion that the ANDA drug's label must remain the same as that of the listed drug," Mensing, 562 F. Supp. 2d at 1062, this court sees it differently.

As the emphasized language suggests, the statement draws the familiar distinction between the near-absolute ban on labeling differences when a manufacturer proposes an ANDA and their availability "after an ANDA is approved." During that latter period, "[t]he applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an [ANDA]," 21 C.F.R. § 314.97, or, as this remark puts it, "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." 57 Fed. Reg. at 17961. That is precisely the process set forth by 21 C.F.R. § 314.70(c)(6)(iii).[32]

[32]Again, as discussed in Part II.B.4, supra, the FDA must approve all labeling changes, even those subject to the CBE process; it is just that such changes, as opposed to their "major" counterparts, are not approved until after the manufacturer has already implemented them.

Accordingly, reading § 314.150 to allow revocation of an ANDA if its holder fails to keep up with warnings added to the listed drug's labeling--rather than if the holder uses the CBE process to add those warnings on its own--harmonizes that regulation with the rest of the FDA's ANDA rules, including §§ 314.70 and 314.97. "Otherwise, the FDA permits a generic manufacturer to strengthen or modify its labeling . . . , only to suspend its approval because the new label does not conform to the label for the listed drug." Barnhill, 2007 U.S. Dist. LEXIS 44718, at *13. This court cannot read the ANDA regulations in such a self-contradictory manner. See, e.g., Ricci v. DeStefano, 129 S. Ct. 2658, 2699 (2009) ("Our task in interpreting separate provisions of a single [enactment] is to give [it] the most harmonious, comprehensive meaning possible.").

***b*. The FDA's contrary amicus briefs and footnote**

As the defendants emphasize, the FDA has made statements since it promulgated the current ANDA regulations to the effect that a generic manufacturer cannot utilize the CBE process to effect a labeling change. Some of these statements were in amicus briefs the FDA filed in Colacicco, supra, first in the district court and later in the Court of Appeals for the Third Circuit. The brief to the Third Circuit, however, was recently withdrawn, with the explanation that "the United States does not

take a position on whether plaintiffs-appellants' claims in this case are preempted. The [FDA] has not yet conducted an examination of various preemption issues following the Supreme Court's decision in Wyeth that would be necessary to inform a position of the United States in this case." Letter from Sharon Swingle, Appellate Staff, DOJ, to Marcia M. Waldron, Clerk, Court of Appeals for the Third Circuit (Apr. 28, 2009) (on file with the Court of Appeals for the Third Circuit).[33]

The defendants also rely on the footnote in the FDA's proposed 2008 revision to § 314.70(c) asserting that "CBE changes are not available for generic drugs approved under an [ANDA] 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." 73 Fed. Reg. at 2849 n.1. But as discussed in Part II.B.4, supra, the footnote does not accompany a proposal to amend § 314.70 in any way that would call for a comment on the availability of its procedures to generic drug manufacturers.[34] Nor was the language of the footnote, in any form, included in the final version of the revision. So "[t]he FDA essentially

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[33]And as discussed in note 27, supra, an agency's statements in amicus briefs receive no particular deference from the courts of this circuit anyway. See Rosenberg, 170 F.3d at 12.

[34]As discussed in Part II.B.4, supra, the proposed (and ultimately the final) rule was "to reaffirm that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information." 73 Fed. Reg. at 2849.

took the opportunity to make a significant statement on the preemption of generic drug labeling claims in the relative obscurity of a footnote in the introductory statement of a document that has nothing at all to do with rules pertaining to generic drugs or to the ANDA process." Denahy, 586 F. Supp. 2d at 654 (emphases deleted).

Based on these concerns, the court in Denahy refused to accord the footnote "any significant level of deference" in deciding whether generic manufacturers can avail themselves of the CBE process for labeling changes. Id. This is consistent with precedent from the court of appeals. An agency's statements that "are neither adjudicatory nor the product of notice-and comment rulemaking . . . are . . . entitled to deference only to the extent they have the power to persuade," an approach known as "Skidmore deference" after Skidmore v. Swift & Co., 323 U.S. 134 (1944). Noviello v City of Boston, 398 F.3d 76, 90 n.3 (1st Cir. 2005) (citing Christensen v. Harris County, 529 U.S. 576, 587 (2000)). The FDA's footnote in its 2008 proposed regulation, which, again, was not incorporated into the final version of the rule and therefore was not subjected to the notice-and-comment procedure, fits this category. See Stacel, 620 F. Supp. 2d at 906; Kellogg, 612 F. Supp. 2d at 435.[35] Thus, "the agency must

[35]Kellogg also observed that "[t]here is no ambiguity in the regulations," since § 314.97 "plainly instructs ANDA holders to comply with § 314.70," and that no deference is therefore due the

ultimately depend on the persuasive power of its argument. The simple fact that the agency has a position, in and of itself, is of only marginal significance." Mayburg v. Sec'y of HHS, 740 F.2d 100, 106 (1st Cir. 1984) (Breyer, J.).

The FDA's footnote-bound position that "CBE changes are not available for generic drugs approved under an [ANDA] under 21 U.S.C. § 355(j)" is not persuasive, for the reasons just explained at length in Part III.B.1.b.i.*a*, supra. First, the footnote did not so much as acknowledge 21 C.F.R. § 314.97. Second, while the footnote did cite § 314.150(b)(10), that rule, as already discussed at length, provides only that the FDA may attempt to withdraw its approval of an ANDA if "the labeling for the drug product that is the subject of the [ANDA] is no longer consistent with that for the listed drug"; it says nothing at all about CBE changes, and cannot be read to prevent them in light of the other provisions of the ANDA rules. Third, while the footnote also cited certain of the agency's comments in promulgating the ANDA regulations, those comments, as also already discussed at length, do not support excluding generic manufacturers from the CBE process. Based on these deficiencies, this court joins with those others that have refused to adopt the

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footnote under Auer v. Robbins, 519 U.S. 452 (1997). This court agrees but, in any event, the defendants do not argue that the rule is ambiguous or that Auer deference applies.

view set forth in the FDA's footnote. See Stacel, 620 F. Supp. 2d at 907; Kellogg, 612 F. Supp. 2d at 435; Denahy, 586 F. Supp. 2d at 655; but see Morris, 2009 WL 424590, at *6 (deferring to the footnote without discussing the appropriate level of deference as a matter of administrative law); Mensing, 562 F. Supp. 2d at 1064 (same).[36]

The defendants nevertheless argue that because, "[i]n codifying FDA's procedures, Congress clearly required generic drug labeling to be the 'same as' the pioneer drug," the FDA's footnote interpreting its regulations to that effect "is not only entitled to deference, but is 'virtually conclusive.'" (quoting Red Lion Broad. Co. v. FCC, 395 U.S. 367, 380-81 (1969)). This court again differs with the defendants' view.

First, while Congress did indeed "generally extend[] the procedures used to approve generic copies of pre-62 drugs to post-62 drugs" through the Hatch-Waxman Amendments, H.R. Rep. No. 98-857, pt. 1, at 1, 1984 U.S.C.C.A.N. at 2647, those Amendments, as is clear by now, did not in fact require the generic drug's labeling to remain the same as the pioneer's drug's post-approval; they required the labeling proposed in the ANDA to be the same as the pioneer drug's. See Part III.B.1.a, supra.

[36]The district court's opinion in Colacicco, supra, also deferred to the footnote, 432 F. Supp. 2d at 537, but, as noted above, that decision, following its affirmance by the Third Circuit, was vacated by the Supreme Court for reconsideration in light of Wyeth. 129 S. Ct. 1578.

Second, the defendants have pointed to nothing in the rules the FDA had in place before Hatch-Waxman indicating that the agency disallowed post-approval changes to the labeling of an ANDA-approved drug. The relevant rules, both before and after their amendment in 1983, required only that an ANDA contain "[l]abeling that is in accord with the labeling conditions described in the finding that an [ANDA] is sufficient." 48 Fed. Reg. at 2756 (later codified at 21 C.F.R. § 314.2(f)(2) (1984)) (emphasis added); see also 35 Fed. Reg. at 6575 (later codified at 21 C.F.R. § 130.4(f)(2) (1971)).

As discussed in Part II.B.2, supra, that "finding" was the first step of the ANDA approval process prior to Hatch-Waxman, and hinged on whether the drug, based on its approval through the DESI process, could be approved in generic form without additional clinical and pre-clinical studies--not on whether the generic drug had the same labeling as its DESI-approved version. See 48 Fed. Reg. at 2751 (later codified at 21 C.F.R. § 314.2(a) (1984)); 35 Fed. Reg. at 6575 (later codified at 21 C.F.R. § 130.4(f)(2) (1971)). It was not until after that finding had issued that the rules placed any restriction on labeling, and even that restriction operated only to keep the labeling proposed in the ANDA "in accord with the labeling conditions described in the finding," as opposed to with those of the pioneer drug.

Given that, as discussed in Part II.B.2, supra, the FDA retained this precise language when it amended its ANDA rules in 1983, that amendment also imposed no such restriction. To the contrary, the amendment simply limited a finding that an ANDA was suitable "to a product that was the same in active ingredient, dosage form and strength, and conditions of use as the drug product that was the subject of the finding." 48 Fed. Reg. at 2755 (later codified at 21 C.F.R. § 314.2(a) (1984)). This amendment did not prevent the FDA from finding, in the first step of the ANDA process, that an ANDA was suitable for a drug with labeling that differed from its DESI-approved version.

So the defendants are incorrect that, in the years prior to Hatch-Waxman, the FDA's rules disallowed ANDAs proposing labels for generic drugs that differed from those of their DESI-approved versions; the rules merely disallowed ANDAs proposing labels not "in accord with the labeling conditions described" in the agency's finding that an ANDA was suitable for that particular drug. Indeed, had FDA rules during that time in fact done what the defendants say, the agency would not have referred to its post Hatch-Waxman rule that an ANDA show "that the proposed labeling for its drug product is the same as that of the reference listed drug" as "a new requirement." 54 Fed. Reg. at 28884 (emphasis added). Even if the defendants were correct, moreover, the most their assertion demonstrates is that, under

the FDA's pre-Hatch-Waxman regime, an ANDA had to propose labeling that was the same as the pioneer drug's. As in the case of the Hatch-Waxman Amendments themselves and the FDA's implementing regulations, it simply does not follow that the labeling had to remain the same after the ANDA had been approved.

***c*. The presumption against pre-emption**

As just discussed in exhaustive detail, that point is clear from the text of the statute and the regulations. But even if the defendants, through the footnote and certain other portions of the FDA comments on its ANDA rules, were able to cast some doubt on whether generic manufacturers can use the CBE process to make labeling changes, that doubt could not be resolved in the defendants' favor. As Wyeth makes clear, a court must "start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." 129 S. Ct. at 1194-95. For the reasons just discussed at length--in particular, the absence of any ban on labeling changes to an ANDA-approved drug in either the Hatch-Waxman Amendments or their implementing rules--that presumption cannot be overcome here.

This is not to say that Congress could not have passed legislation to give the FDA, rather than state authorities or juries, the final say-so on the content of generic drug labeling,

much as Congress has done in the case of medical devices. See id. at 1200 (citing Riegel v. Medtronic, Inc., 128 S. Ct. 999 (2008)). It is just that, without evidence of such a "clear and manifest purpose" to pre-empt state law, this court must presume that federal law is not to be read to that effect. The defendants cannot overcome that presumption here, even if any and all arguable inconsistencies in the FDA's commentary are resolved in the defendants' favor. See Stacel, 620 F. Supp. 2d at 906-07; Kellogg, 612 F. Supp. 2d at 436; but see Mensing, 562 F. Supp. 2d at 1061 (declining to apply the presumption, pre-Wyeth).

ii. Even read as the defendants suggest, the regulations do not make compliance with state law impossible

Finally, even if the defendants were correct that they could not use the CBE process to make unilateral changes adding or strengthening warnings to their generic drug, it does not follow that compliance with state law requiring such warnings is impossible. In Wyeth, the Court rejected the drug manufacturer's argument that "if it had unilaterally added . . . a warning, it would have violated federal law governing unauthorized distribution and misbranding . . . on the assumption that this labeling change would have rendered [its drug] a new drug lacking an effective application." 129 S. Ct. at 1197.

The Court reasoned, first, "strengthening the warning would not have rendered [the manufacturer's drug] a new drug" (citing 21 U.S.C. § 321(p)(1) and 21 C.F.R. § 310.3(h)) and, second,

> Nor would this warning have rendered [the drug] misbranded. The FDCA does not provide that a drug is misbranded simply because the manufacturer has altered an FDA-approved label; instead, the misbranding provision focuses on the substance of the label and, among other things, proscribes labels that fail to include 'adequate warnings.' 21 U.S.C. § 352(f). Moreover, because the statute contemplates that federal juries will resolve most misbranding claims, the FDA's belief that a drug is misbranded is not conclusive.

Id. (emphasis added).

The same reasoning applies with equal force here. Even if § 310.150(b)(10) forbids a generic manufacturer from using the CBE procedure to strengthen its label, the FDA would have to enforce that prohibition through proceedings to withdraw its approval of the ANDA under 21 U.S.C. § 355(e). Like the misbranding trials discussed by the Court in Wyeth, the outcome of such a proceeding ultimately turns not on whether the label is in fact "consistent with" that of the listed version, but on whether "such drug is unsafe under the conditions of use upon the basis of which the application was approved" or "there is lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. §§ 355(e)(1), (3). So, even if the defendants were

correct that § 314.150(b)(10) required them to keep the same label on their generic Sulindac as that on the listed version, it is hardly a foregone conclusion that breaking the rule by strengthening a particular warning without prior FDA approval would result in revocation of their ANDA for the drug.[37]

The upshot is that, at best, the defendants can show "a hypothetical or potential conflict . . . insufficient to warrant pre-emption." Rice v. Norman Williams Co., 458 U.S. 654, 659 (1982). The defendants have offered no reason to believe that the FDA would begin revocation proceedings against them for strengthening the warning, and no reason to believe that those proceedings would actually lead to revocation under § 355(e). They have not met the demands of impossibility pre-emption. See Wyeth, 129 S. Ct. at 1197-98; Kellogg, 612 F. Supp. 2d at 430.

[37]There is also the Wyeth Court's point that "the very idea that the FDA would bring an enforcement action for strengthening a warning pursuant to the CBE is difficult to accept--neither [the defendants] nor the United States has identified a case in which the FDA has done so." 129 S. Ct. at 1197. Thus, while non-enforcement of a prohibition does not necessarily have any legal consequence, the Court in Wyeth reasoned that the historical lack of a misbranding prosecution arising out of a strengthened warning at least tended to undermine the manufacturer's impossibility argument.

2. Frustration-of-purpose pre-emption

The defendants also claim that the state law underlying the plaintiffs' failure-to-warn claims "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" in the Hatch-Waxman Amendments. Good, 501 F.3d at 47. Specifically, the defendants argue that state-law requirements that a manufacturer alter the warning on an ANDA-approved drug post-approval will necessarily entail duplicative clinical trials "necessary to generate the data that might put generic companies on notice that label changes are warranted." This testing, the argument goes, will drive up the price of generic drugs in contravention of one of Hatch-Waxman's goal "to make available more low cost generic drugs by establishing a generic drug approval procedure for drugs approved after 1962." H.R. Rep. No. 98-857, pt. 1, at 14, 1984 U.S.S.C.A.N. at 2647. There are a number of serious problems with this argument.

At the outset, the defendants do not identify anything in the statutory or regulatory provisions on manufacturing changes, 21 U.S.C. § 356a and 21 C.F.R. § 314.70, requiring that manufacturers justify heightened warnings with the results of their own clinical trials. Those provisions, in fact, contain no such requirement. See 21 U.S.C. §§ 356a(d)(3)(A), 21 C.F.R. § 314.70(c)(3). And another FDA rule, as discussed in Part II.B.5, supra, requires that "labeling shall be revised to

include a warning as soon as there is reasonable evidence of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e). If anything, then, the regulatory scheme actually contemplates that manufacturers add warnings to their labels without conducting clinical trials; it in no way makes those trials a prerequisite to such additions. So the premise of the defendants' argument is defective.

Furthermore, as also discussed in Part II.B.5, supra, FDA rules enacted to carry out the Hatch-Waxman Amendments specifically require ANDA holders to adhere to the agency's rules on "the reporting and recordkeeping of adverse drug experiences," 21 C.F.R. § 314.98(a), which include, among other things, a mandate for "written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA," id. § 314.80(b). These requirements naturally impose costs on generic drug makers, driving up the costs of their products. Yet the FDA has chosen to subject generic manufacturers to its monitoring and reporting requirements anyway. This strongly suggests that the similar requirements of state products liability law do not stand as an obstacle to Hatch-Waxman's cost-cutting objectives.[38]

[38]A different kind of state-law claim could theoretically have this effect: for example, a claim that a manufacturer of an ANDA-approved drug was negligent in failing to conduct clinical trials prior to its approval. But that is not this case, where the Bartletts allege that "reports of serious adverse events

As discussed in Parts II.B.1-2, supra, Congress pursued those objectives through the Hatch-Waxman Amendments by relieving generic drug manufacturers of the burdens of safety and effectiveness testing as a condition of approval. The defendants have pointed to nothing in the Amendments, their legislative history, the FDA's rules enforcing them, or the agency's comments in making those rules to indicate that Congress also sought to relieve generic drug manufacturers of any of the burdens of state products liability law. There is little doubt that doing so would likewise reduce the cost of generic drugs, but it does not follow that Congress intended that state laws having the opposite effect should perish on the strength of Hatch-Waxman.[39]

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associated with Sulindac . . . in the medical literature"--rather than independent testing--sufficed to put the defendants on notice that a stronger warning was appropriate.

[39]The defendants' reliance on Justice Breyer's concurring opinion in Wyeth is therefore misplaced. He noted that "some have argued that state tort law can sometimes raise prices to the point where those who are sick are unable to obtain the drugs they need" and that, in such a case, the FDA may determine that state tort law serves as "a hindrance to achieving the safe drug-related medical care that Congress sought." 129 S. Ct. at 1204. Thus, Justice Breyer observed, the FDA "may seek to embody those determinations in lawful specific regulations describing, for example, when labeling requirements serve as a ceiling as well as a floor. And it is possible that such determinations would have pre-emptive effect." Id. The defendants, however, point to nothing to suggest that either Congress or the FDA determined that state tort law--as opposed to federal drug-approval requirements--was acting as a hindrance to "safe drug-related medical care" by driving up generic drug prices. Thus, whatever the proper reading of FDA rules as they govern labeling changes to ANDA-approved drugs, those rules do not "embody" any

As the court of appeals has instructed, "it is not the fact of [federal] action on a particular subject alone--but the reasons for the action--that control its preemptive effect." Good, 501 F.3d at 55. Lacking any evidence that Congress passed the Hatch-Waxman Amendments intending to displace state-law labeling requirements on generic drugs, the defendants have provided no basis for finding those requirements pre-empted by the Amendments. Nor have the defendants overcome the assumption, endorsed by the Wyeth Court, that "[i]f Congress thought that state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision" directed at those suits as part of Hatch-Waxman. 129 S. Ct. at 1199. Here, as there, the fact that Congress did no such thing strongly indicates that Congress meant to do no such thing. Again, "the purpose of Congress is the ultimate touchstone in every pre-emption case." Id. at 1194 (internal quotation marks omitted).

In that vein, the defendants' frustration-of-purpose argument (and their impossibility argument, for that matter) raises another serious difficulty: leaving those injured by drugs unaccompanied by warnings deemed adequate by state law without any remedy at all without any indication that Congress desired, or even contemplated the possibility, of such a

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determination to displace state tort law. So Justice Breyer's observations are inapposite here.

result.[40] While Congress could have thought this a necessary consequence of lowering the costs of prescription drugs, "[i]f Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly." Bates v. Dow Agrosciences LLC, 544 U.S. 431, 449 (2005).

But, as just discussed at length, Congress did not do so. Without such a clear expression of intent, this court refuses to take that step on its own. This puts this court in line with others to consider the issue. See Stacel, 620 F. Supp. 2d at 907; Kellogg, 612 F. Supp. 2d at 440-41; Schrock v. Wyeth, Inc., 601 F. Supp. 2d 1262, 1265-66 (W.D. Okla. 2009); Laisure-Radke,

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[40]The vast majority of courts have rejected the notion that the manufacturer of the brand-name drug may be liable for defects in its generic equivalent on a theory of "innovator liability." See, e.g., Foster, 29 F.3d at 171; Goldych v. Eli Lilly & Co., No. 04-1477, 2006 WL 2038436, at *6 (N.D.N.Y. July 19, 2006); Colaccio, 432 F. Supp. 2d at 543; Block v. Wyeth, Inc., No. 02-1077, 2003 WL 203067, at *2-*3 (N.D. Tex. Jan. 28, 2003); Sharp v. Leichus, No. 2004-0643, 2006 WL 515532, at *3-*5 (Fla. Cir. Ct. Feb. 17, 2006); Kelly v. Wyeth, No. 2003-03314, 2005 WL 4056740, at *4 (Mass. Super. Ct. May 6, 2005); but see Conte v. Wyeth, Inc., 85 Cal. Rptr. 3d 299, 318 (Cal. Ct. App. 2008). While this court need not decide whether New Hampshire would recognize such a theory, its widespread rejection supports the view that, if failure-to-warn claims against generic drug makers are indeed pre-empted, those injured as a result of deficient warnings on those products have no recourse. The defendants did not dispute this point at oral argument, suggesting instead that consumers who opt for generic drugs over name-brand equivalents may have effectively lost their right to recompense for injuries suffered from inadequate warnings in the bargain. That suggestion is not only distasteful but also contrary to fundamental principles of tort law.

2006 WL 901657, at *6; accord Foster, 29 F.3d at 170 ("The statutory scheme governing premarketing approval for drugs simply does not evidence Congressional intent to insulate generic drug manufacturers from liability . . . or . . . to alter state products liability law"). The defendants have not shown that the state-law requirements underlying the Bartletts' failure-to-warn claims present an obstacle to the accomplishment and execution of the full purposes and objectives of Congress in the Hatch-Waxman Amendments or their implementing regulations.

III. Conclusion

For the foregoing reasons, the defendants' motion for judgment on the pleadings is DENIED.

SO ORDERED.

Joseph N. Laplante
United States District Judge

Dated: September 30, 2009

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