UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

WYETH PHARMACEUTICALS,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Civil Action No. 09-1810**
	)	
U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,	)	
	)	
Defendants.	)	
	)	

MEMORANDUM OPINION AND ORDER

Before the Court is Plaintiff Wyeth Pharmaceutical's ("Wyeth's") motion for a temporary restraining order ("TRO") [Dkt. 2] requiring the Food and Drug Administration ("FDA") to withdraw or suspend the FDA's approval of the Abbreviated New Drug Applications ("ANDAs") submitted by Orchid Healthcare ("Orchid") and to halt the distribution and use of Orchid's generic drug. These ANDAs, approved on September 15, 2009, sought to market generic formulations of piperacillin sodium-taxobactam sodium, marketed and sold by Wyeth as Zosyn® ("Zosyn"). Wyeth argues that Orchid's drug is materially different from Zosyn and that the FDA acted arbitrarily and capriciously by approving Orchid's generic drug for distribution. Because Wyeth has failed to demonstrate a likelihood of success on the merits, the Court denies Wyeth's motion.

FACTUAL BACKGROUND

Wyeth is a pharmaceutical manufacturer that markets and sells the drug Zosyn, an intravenous antibiotic drug used to treat moderate to severe bacterial infections. (Compl. ¶ 2.) The original formulation of Zosyn, approved by the FDA in 1993 and sold by Wyeth until 2005 or later, was incompatible for use with certain other products, including Lactated Ringer's Solution ("LRS"), a diluent and fluid resuscitation agent. (Mem. of P. & A. In Support of Pl.'s Mot. for a Prelim. Inj. or, In the Alternative, a T.R.O. ["Pl.'s Mem."] at 3, 9, 11.) The label for the original Zosyn included a prominent warning stating that LRS was not compatible with Zosyn. (*Id.* at 9) The original formula was also vulnerable to the formation of particulates which, if present in excess quantities, can cause adverse health events. (Decl. of David Wu, M.D. ¶¶ 20-30.) When the FDA expressed concern as to the amount of particulate matter found in batches of Zosyn, Wyeth conducted research and determined that it could inhibit particulate formation by adding two inactive ingredients, edetate disodium dihydrate ("EDTA") and citric acid monohydrate, to the Zosyn formula. (*Id.* ¶¶ 31-33.) Additional studies also revealed that the addition of EDTA and citric acid to Zosyn made the drug compatible with LRS. (*Id.* ¶ 34.) In 2005, the FDA approved a supplemental New Drug Application for the reformulated Zosyn, which Wyeth began to market with a new label, reflecting its compatibility with LRS. (*Id.* ¶¶ 37-38.) Wyeth then phased out the old formulation of the drug, and currently, only the new formulation of Zosyn is in use in the United States. (*Id.* ¶¶ 38-40.)

The FDA is a federal agency that regulates prescription drugs under authority delegated by Congress and the Secretary of Health and Human Services. (Compl. ¶ 18.) In 2006, Orchid, a pharmaceutical company, filed ANDAs with the FDA seeking approval for a generic version of Zosyn based on the drug's original formula—that is, without the addition of the inactive

ingredients EDTA and citric acid. (Compl. ¶ 63, 66.) Orchid and other drug manufacturers also submitted citizen petitions requesting a determination from the FDA that the original formulation of Zosyn was not discontinued for reasons of safety and efficacy. (*Id.* ¶ 62; Decl. of Bradford A. Berenson ["Berenson Decl."], Ex. 15 at 1.) Wyeth opposed Orchid's ANDAs, arguing that under FDA regulations, a generic injectable drug must generally contain the same inactive ingredients as the "reference drug," and that the generic Zosyn, without EDTA and citric acid, did not meet this standard. (Berenson Decl., Ex. 3 at 12.) As such, Wyeth argued that the use of the generic without some form of risk minimization action plan ("RiskMAP") would have adverse consequences. (*Id.* at 13-17.)

On September 15, 2009, the FDA granted the petitions from Orchid and other pharmaceutical companies, finding that the original Zosyn formulation was not discontinued for reasons of safety or efficacy. (Berenson Decl., Ex. 15 at 19.) The FDA also accepted and approved Orchid's ANDAs for piperacillin and taxobactam for injection. (*Id.*) In approving Orchid's ANDAs, the FDA found that although Orchid's generic Zosyn is not compatible with LRS, the product's warning label notes this incompatibility, and that as a result, the drug is "as safe and effective as Wyeth's reformulated Zosyn under the labeled conditions of use." (*Id.* at 6.) In particular, the FDA cited "experience with Wyeth's original Zosyn formulation and FDA's recent analysis" in support of its conclusion that the inactive ingredients in Orchid's generic version, while different from those in the current Zosyn formula, are safe. (*Id.* at 11.) The FDA went on to state that

> [b]ecause the original Zosyn formulation clearly meets the statutory safety standard with respect to inactive ingredients, the Agency may rely on § 314.99(b) to grant a waiver of the regulation requirement that the ANDA formulation contain the same inactive ingredients in the same concentration with the limited exceptions for preservatives, buffers, and antioxidants.

(*Id.* at 12; *see also* 21 C.F.R. §§ 314.94(a)(9)(iii), 314.99(b).)

The FDA also found that differences between the label on the current formulation of Zosyn, advertising its compatibility with LRS, and the label on Orchid's product, noting its incompatibility, were acceptable. (Berenson Decl., Ex. 15 at 13.) The Agency cited FDA regulations allowing differences in labels for generic drugs and corresponding reference listed drugs based on, among other things, formulation. (*Id.*; *see also* 21 C.F.R. 314.94(a)(8)(iv).) The FDA reasoned that the generic drug's incompatibility with LRS, requiring a warning not present on the reformulated Zosyn, was a result of the generic drug's formulation without the inactive ingredients EDTA and citric acid. (Berenson Decl., Ex. 15 at 13.)

On September 22, 2009, a full week after the FDA's approval of Orchid's generic drug, Wyeth filed its complaint, a motion for a TRO, and a 50-page memorandum of law with some 350 pages of attachments, alleging that the FDA's action violates the Federal Food, Drug, and Cosmetic Act ("FDCA"), the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"), FDA's implementing regulations, and the Administrative Procedure Act ("APA"). (Compl. ¶¶1, 8-9.) Specifically, Wyeth asserts that the FDA's approval of generic Zosyn violates the same-ingredients requirement, 21 C.F.R. § 314.94(a)(9)(iii), and the same-labeling requirement, 21 U.S.C. § 355(j)(2)(A)(v), and that the FDA failed to meaningfully consider alternatives such as risk management plans to communicate to physicians and patients the difference in terms of how the drug can be administered between Zosyn and the generic. (Pl.'s Mot. at 2-3.) Wyeth argues the generic version "cannot be safely administered in essentially the same way as the innovator drug" and creates a significant risk of medication errors and patient harm. (*Id.* at 3.) Accordingly, Wyeth contends that absent intervention by this Court, distribution and use of the generic drug will put the lives of patients at risk and cause

Wyeth irreparable financial and reputational harm. (*Id.* at 3.) Accordingly, Wyeth seeks a TRO requiring the FDA to withdraw or suspend its approval of the generic Zosyn. (*Id.* at 2.)

On a September 23 conference call with the parties and anticipated intervenors Orchid and Apotex Inc. ("Apotex"),[1] the Court learned from counsel for Apotex that the generic product had already been shipped to wholesalers and to hospitals and perhaps had entered the chain of commerce as of September 22, 2009, and would likely be in use in hospitals within days. As a result, Wyeth broadened its earlier request and asked the Court to issue an immediate TRO, suspending or revoking the FDA's approval of the generic so that further distribution and hospital use would be stopped.

LEGAL ANALYSIS

I. STANDARD OF REVIEW

The APA entitles "[a] person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action . . . to judicial review therof." 5 U.S.C. § 702. A reviewing court must set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.* § 706(2)(A); *Tourus Records, Inc. v. DEA*, 259 F.3d 731, 736 (D.C. Cir. 2001). In determining whether an agency violated § 706, the Court performs "only the limited, albeit important, task of reviewing agency action to determine whether the agency has conformed with controlling statutes and whether the agency has committed a clear error of judgment." *Zeneca, Inc. v. Shalala*, 213 F.3d 161, 167 (4th Cir. 2000) (internal quotation omitted); *see also Marsh v. Or. Natural Res. Council*, 490 U.S. 360, 378

[1] Apotex has exclusive rights over the distribution of the generic form of Zosyn. Based on its conference call with the parties, the Court understands that Wyeth has no objection to the intervention of Orchid, but it has not yet taken a position with respect to Apotex.

(1989). "Where the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, we must undo its action." *County of Los Angeles v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999) (quoting *BellSouth Corp. v. FCC*, 162 F.3d 1215, 1222 (D.C. Cir. 1999)). However, "[t]he scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Rather, agency action is "entitled to a presumption of regularity." *Citizens to Pres. Overton Park v. Volpe*, 401 U.S. 402, 415 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977).

II. TEMPORARY RESTRAINING ORDER

In seeking injunctive relief, a plaintiff "must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 129 S. Ct. 365, 374 (2008). Without a "substantial indication" of likely success on the merits of an action, "there would be no justification for the court's intrusion into the ordinary processes of administration and judicial review." *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 38 F. Supp. 2d 114, 140 (D.D.C. 1999) (quoting *Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 (D.C. Cir. 1977)). Injunctive relief "is an extraordinary and drastic remedy" and "should not be granted unless the movant, *by a clear showing*, carries the burden of persuasion." *Mazurek v. Armstrong*, 520 U.S. 968, 972 (1997) (internal quotation omitted); *see also Astellas Pharma U.S., Inc. v. FDA*, No. 09-1511, 2009 WL 2488901, at *4 (D.D.C. Aug. 12, 2009) ("As an extraordinary remedy, courts should grant [TROs] sparingly.").

Mindful of the deference due the FDA, especially given its expertise in this complex area and the heavy burden imposed on a plaintiff, *see*, *e.g.*, *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997), the Court concludes that Wyeth has failed to make a sufficient showing of a substantial likelihood of success on the merits.[2] In reaching this conclusion, the Court has reviewed plaintiff's pleadings as carefully as possible under the time constraints imposed by plaintiff, specifically focusing on those portions designated by the parties during the conference call; the proposed intervenors' opposition to the motion that was filed last evening; and the relevant law.

Plaintiff makes three arguments for invalidating the FDA's decision:

a. The FDA's approval of the generic version of Zosyn violates the same ingredients requirement. (Pl.'s Mot. at 2.) According to Wyeth, since the generic version of Zosyn is based on a superseded formulation that does not share the same drug compatibility profile as Wyeth's branded product and cannot be co-administered with LRS, the generic drug creates a risk of harm to the patient because of the possibility of confusion and medication error. (Pl.'s Mem. at 1) Wyeth asserts that the FDA erred by ignoring Wyeth's expert testimony, by finding that the difference in the generic and branded formulas did not affect safety (contrary to 21 C.F.R. § 314.94(a)(9)(iii)), and by considering the safety of the generic drug divorced from the changed circumstances created by the reformulated drug's compatibility with LRS. (*Id.* at 4-6.)

b. The FDA misinterpreted the Hatch-Waxman Act, 21 U.S.C. § 355(j)(2)(A)(v), when it permitted differences in labeling by relying on the "formulation" exemption set forth in 21 C.F.R. 314.94(a)(8)(iv). (Pl.'s Mot. at 3; Pl.'s Mem. at 6.)

c. The FDA erred by not requiring the generic manufacturer to implement a risk management action plan, or "RiskMAP," to mitigate the risks of harm

[2] Since the Court concludes that the plaintiff has failed to make a clear and convincing showing that it will succeed on the merits, it need not address the remaining factors except to note that a TRO will impose significant economic harm on the intervenors since they have already begun marketing the generic drug pursuant to Orchid's grant of an exclusivity period of 180 days, *see* 21 U.S.C. § 355(j)(5), and it is far from clear on the record that the denial of a TRO will cause irreparable harm to the plaintiff or the public. (*See* Berenson Decl., Ex. 15 at 9, 16 n.36.)

> to patients from possible product confusion and medication error. (Pl.'s Mot. at 3; Pl.'s Mem. at 37.)

While plaintiff's argument is presented as a three-pronged attack, the gravamen of Wyeth's complaint is that the FDA erred by ignoring Wyeth's evidence relating to the health risks posed by permitting a generic to be marketed simultaneously with a reformulated product where the warning label on the generic must caution against use with LRS, but no such warning is needed for the reformulated drug. Contrary to plaintiff's argument, the FDA specifically considered plaintiff's evidence as to the risk of harm and rejected it as "speculative and conclusory in nature." (Berenson Decl., Ex. 15 at 17 n.38.) The FDA also noted that plaintiff had simultaneously marketed, without problem, both the original formulation and the reformulated product for "some period of time." (*Id.* at 5, 9.) Finally, the FDA endorsed the reasoning from the district court's opinion in *Zeneca Inc. v. Shalala*, No. 99-307, 1999 WL 728104 (Aug. 11, 1999 D. Md.), when rejecting Wyeth's attack on the efficacy of the warning label on the generic drug. (Berenson Decl., Ex. 15 at 17 n.38). As Judge Nickerson aptly observed in *Zeneca*:

> The Court finds curious Zeneca's related argument that the warnings are ineffective to render Gensia's product safe because physicians will ignore those warnings. . . . Regulations related to the labeling and packaging of drugs are a fundamental part of FDA's regulatory scheme. To assume that health care providers would either fail to read or ignore clear warnings would call into question that entire scheme. Zeneca has provided no support for this remarkable assertion. As to Zeneca's claim that the warnings are not sufficiently clear, that they should be printed in a bolder print or a different color, that is precisely the kind of specialized determination about which this Court cannot substitute its judgment for that of the regulatory agency.

1999 WL 728104, at *9. This same degree of skepticism applies equally well in this case.

Moreover, the case law fully supports granting *Chevron* deference to the FDA's interpretation of the Hatch-Waxman Act and the relevant regulations. *See Chevron v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984). As found by the Fourth Circuit on appeal in *Zeneca v. Shalala*, the FDA's construction of "formulation" with respect to labeling is not plainly erroneous but is consistent with its own regulations.[3] *Zeneca*, 213 F.3d at 169; *see also Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). Similarly, as found in the *Zeneca* case, the FDA correctly concluded that differences in the inactive ingredients between the generic drug and the reformulated drug do not affect the safety of the generic drug within the meaning of 21 C.F.R. § 314.94(a)(9)(iii). *See Zeneca*, 23 F.3d at 168 ("Specifically, the language of sections 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) is broad enough to encompass the FDA's interpretation. Furthermore, the FDA's interpretation is completely faithful to the statute that these two regulations were promulgated to implement, 21 U.S.C. § 355(j)(4)(H)."). As found by the FDA, the "original Zosyn formulation was and continues to be safe and effective under the labeled conditions of use, and was not discontinued for reasons of safety or effectiveness." (Berenson Decl., Ex. 15 at 9.) Therefore, according to the FDA's decision, the generic drug, with appropriate warnings against use with LRS, would also be safe and effective, as had been the case when Wyeth marketed both versions simultaneously. (*Id.* at 9-11.)

As has been recognized in this jurisdiction, as well as in the Fourth Circuit, risk to the public is negated by the fact that the generic "contains a clear warning label specifying that the drug product" could cause adverse health effects if administered improperly. *Bristoll-Myers*

[3] The Court disagrees with Wyeth's assertion that the *Zeneca* case was "incorrectly decided" by the Fourth Circuit, and any factual distinctions between the two cases do not detract from the persuasiveness of the court's opinion, particularly given the FDA's finding that evidence of the risks presented by the simultaneous use of Zosyn and the generic drug is "speculative." (Pl.'s Mem. at 36; Berenson Decl., Ex. 15 at 17 n.38)

Squibb Co. v. Shalala, 923 F. Supp. 212, 222 (D.D.C. 1996); *see also Zeneca*, 23 F.3d at 167-68. While it is true that the generic here has a different risk profile because it is not compatible with LRS, the FDA reasonably concluded that this risk can be mitigated by an appropriate warning, and it is *not* this Court's job to substitute its judgment for that of the FDA regarding the adequacy of the labeling or the safety of the drug. *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995) ("FDA's 'judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merit deference from us.'") (quoting *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995)).[4]

Accordingly, plaintiff's motion for a TRO is **DENIED.** The parties are directed to contact the chambers of the undersigned on September 28, 2009, at 12:00 p.m. to provide an update on the status of the case.

/s/
ELLEN SEGAL HUVELLE
United States District Judge

Date: September 24, 2009

[4] Given the Court's conclusion regarding the FDA's safety determinations and its acceptance of the warning labels, Wyeth lacks any basis upon which to argue for a TRO based on the agency's failure to impose the requirement of a risk management plan. (Pl.'s Mem. at 37.)