IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

WYETH PHARMACEUTICALS, Plaintiff, v. U.S. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	Civil Action No.

MEMORANDUM OF POINTS AND AUTHORITIES
IN SUPPORT OF PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION OR, IN THE ALTERNATIVE, A TEMPORARY RESTRAINING ORDER

Bradford Berenson (D.C. Bar No. 441981)
Colleen Klasmeier (DC Bar No. 465050)
Gary L. Veron (D.C. Bar No. 445450)
Peter S. Choi (D.C. Bar No. 496780)
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
(202) 736-8000

Attorneys for Plaintiff
Wyeth Pharmaceuticals

Geoffrey Levitt (DC Bar No. 358633)
Wyeth Pharmaceuticals
500 Arcola Road
Collegeville, PA 19426

Of Counsel

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

REGULATIONS

MISCELLANEOUS

Plaintiff Wyeth Pharmaceuticals ("Wyeth"), through undersigned counsel, respectfully submits this Memorandum of Points and Authorities in support of its motion for a preliminary injunction or, in the alternative, a temporary restraining order directing the U.S. Food and Drug Administration ("FDA" or the "Agency"), the U.S. Department of Health and Human Services, Kathleen Sebelius, in her official capacity as Secretary of Health and Human Services, and Margaret Hamburg, M.D., in her official capacity as Commissioner of Food and Drugs (collectively "Defendants") to withdraw or suspend FDA's approval of a generic formulation of the drug Zosyn® ("Zosyn") that is not substantially the same as Wyeth's branded Zosyn in composition, conditions of administration, and approved labeling as required under the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. §§ 301-399), the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"), and FDA's implementing regulations (21 C.F.R. pt. 314).

If the generic approval is not enjoined, a generic version of Zosyn will imminently enter the stream of commerce. That generic version cannot safely be administered in the same manner as the branded product now on the market. In particular, unlike the branded version of Zosyn now in use throughout the United States, it cannot safely be co-administered with Lactated Ringer's Solution, a commonly used fluid resuscitant that is co-administered with Zosyn to tens of thousands of patients experiencing septic shock each year. Because health care providers will mistakenly assume that the generic and branded drugs are interchangeable, as is normally the case, inevitable errors in administration will put the health, safety, and indeed lives of critically ill patients at risk. Wyeth will also suffer irreparable financial and reputational harm as a result of FDA's unlawful decision to allow this situation to occur. The FDA will not be materially harmed by entry of an injunction, but patients will likely suffer grievous and irreparable injury if

this Court permits the generic formulation to enter the market before it has had an opportunity to adjudicate the merits of this action. This Court should therefore enter a preliminary injunction or, in the alternative, a temporary restraining order requiring FDA to withdraw or suspend approval of the generic version of Zosyn.

INTRODUCTION AND SUMMARY OF ARGUMENT

This action arises out of FDA's decision to approve a generic version of Zosyn (piperacillin sodium and tazobactam sodium) that is materially different from the branded product manufactured by Wyeth and currently marketed nationwide. These differences affect the generic version's chemical composition; drug-to-drug interactivity profile and conditions of administration; and approved labeling. Because of these differences, the introduction of this generic product into the marketplace alongside branded Zosyn presents serious risks of confusion and medication error that threaten grave harm to patient health and safety. To Wyeth's knowledge, this is the first time that the FDA has ever approved a generic pharmaceutical that cannot safely be administered in essentially the same way as the innovator drug.

Because generic drug approvals are based on the pre-clinical and clinical safety and efficacy data generated by the innovator drug manufacturer, healthcare professionals and patients expect generic drugs to be equivalent to, and freely interchangeable with, their branded counterparts. When material differences exist—as they indisputably do here—serious issues of drug safety and efficacy are raised. This is exactly the situation that the relevant statutes and FDA's own implementing regulations were designed to prevent. In choosing to ignore the public health risks in this situation and violate these important mandates, FDA has acted arbitrarily, capriciously, and contrary to law.

Zosyn is an intravenous antibiotic drug product indicated for the treatment of moderate to severe bacterial infections. Like many other antibiotic drug products, Zosyn is frequently used in

combination with other drug products, especially in acute and intensive care medical settings. Of central relevance here, Zosyn is frequently co-administered with Lactated Ringer's Solution ("LRS"), a diluent and fluid resuscitation agent, in patients suffering from septic shock.

The generic version of Zosyn approved by FDA is based on a superseded formulation that does not share the same drug compatibility profile as Wyeth's branded product. In particular, it cannot be safely co-administered with LRS, because the LRS deactivates the antibiotic in the generic version of the drug.

As demonstrated in the administrative record and in the papers supporting this motion, the fact that the approved generic version of Zosyn cannot be safely interchanged with the branded version marketed by Wyeth under all foreseeable conditions of use poses serious public health risks. Healthcare professionals and patients rely on FDA to approve generic drugs that share the same safety and efficacy profile and can be used in the same manner as the branded counterpart. The law guarantees that doctors, nurses, and patients may so rely, as the Hatch-Waxman Act requires a generic drug to be "the same" as the branded counterpart in all material respects. *See* H.R. Rep. No. 98-857(I), at 21 (1984) *reprinted in* 1984 U.S.C.C.A.N. 2647 ("[T]he focus of the [Hatch-Waxman amendments] is to provide the Food and Drug Administration with sufficient information to assure that the generic drug is the same as the listed drug."). The standards for parenteral drugs such as Zosyn are especially high, since these drugs are injected directly into a patient, and any differences in a generic product can cause serious and immediate adverse health effects. *See, e.g.,* Abbreviated New Drug Application Regulations (Proposed Rule), 54 Fed. Reg. 28872, 28883 (July 10, 1989) (codified at 21 C.F.R. pts. 10, 310, 314, 320) (FDA intended "to place more stringent limitations on the variations permitted in the inactive ingredients in the formulation of parenteral" drugs because parenteral

drugs are more sensitive to formulation changes). FDA's own public education materials describe a generic drug as "a copy that is *identical* to a brand-name drug in . . . how it is taken, quality, performance, and intended use." *See* FDA, "Generic Drugs: What Everyone Should Know" (Apr. 30, 2009), *available at* <http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm134154.htm> (emphasis added). Because healthcare professionals are entitled to assume that generic and branded drugs are freely interchangeable, they generally do not scrutinize the generic and branded drugs for differences. *See, e.g., Conte v. Wyeth, Inc.*, 168 Cal. App. 4th 89, 107 (Cal. Ct. App. 2008) ("[W]e find the conclusion inescapable that ... a significant number of patients whose doctors rely on [brand name] product information ... are likely to have generic [product] prescribed or dispensed to them."). That is especially true in acute and critical care settings such as emergency rooms, where simultaneous co-administration of Zosyn and LRS is common.

Here, however, there are significant differences between the generic and branded versions of Zosyn that relate to drug-to-drug interactivity and conditions of administration. These differences create a significant risk, supported by substantial evidence in the administrative record, that the generic version of Zosyn will be used in situations that are improper, *i.e.*, where compatibility with LRS is mistakenly believed to exist based on years of experience using the reformulated version of Zosyn marketed by Wyeth. As a result of these medication errors, drug deactivation may occur in very ill patients who are desperately in need of antibiotic treatment. This is precisely the sort of situation the fundamental "sameness" requirement in the statutory scheme was intended to prevent.

FDA's decision to approve a generic version of Zosyn characterized by such significant and potentially dangerous differences with the branded product is arbitrary, capricious, and

contrary to law. The FDA's decision is infected throughout by a fundamental conceptual and legal error: the belief that it may ignore the type of risk to public health that arises from the possibility of confusion and medication error when non-equivalent generic and branded products are in the marketplace simultaneously. Nowhere in its decision to approve the generic formulation does FDA meaningfully address this risk or the evidence supporting it, which lay at the heart of Wyeth's objection to the generic applications. Instead, ignoring the real issue in this case, each significant aspect of FDA's decision simply assumes that it may evaluate the safety of the generic in isolation based on its intrinsic safety for uses described in the generic labeling, without regard to how differences in labeling and composition that are expressly prohibited by statute or regulation might make the drug unsafe for use in clinical practice. The statutes and regulations governing generic drug approvals do not permit this blinkered approach.

First, for parenteral drugs, the law generally requires that the generic drug have the same active and inactive ingredients in the same concentrations as the branded drug. 21 U.S.C. §§ 355(j)(2)(A)(ii)(I), 355(j)(4)(H); 21 C.F.R. § 314.94(a)(9)(iii). The approved generic version of Zosyn violates this requirement, because it does not contain the new inactive ingredients added to reformulated Zosyn: EDTA and citric acid. Although narrow exceptions are allowed for an inactive ingredient that functions as a "preservative, buffer, or antioxidant" and is proven not to affect safety, 21 C.F.R. § 314.127(a)(8)(ii)(B), EDTA functions as a metal-ion chelating agent—not a preservative, buffer, or antioxidant—in the reformulated version of Zosyn. And citric acid, although a buffer, indisputably affects safety, because it plays an important role in controlling particulate levels and influencing the drug-to-drug compatibility profile of Zosyn. The FDA's decision to waive these requirements without regard to the documented risk of medication error was arbitrary and capricious, and the FDA's action violates the "same ingredient" requirement for

generic drug approvals. *See* 21 C.F.R. §§ 314.94(a)(9)(iii), 314.127(a)(8)(ii)(A)-(B); *see also* 54 Fed. Reg. at 28884 ("the agency will presume any inactive ingredient in an applicant's proposed drug product different from that in the reference listed drug to be unsafe unless the applicant can rebut the presumption by demonstrating that the different inactive ingredient will not affect the safety of its proposed drug product.").

Second, the Hatch-Waxman Act requires that generic drugs have "the same" labeling as the branded counterpart. 21 U.S.C. § 355(j)(2)(A)(v). The labeling for the approved generic version of Zosyn, however, includes a warning against simultaneous co-administration with LRS that is not found in the labeling for Wyeth's branded formulation. Thus, the labeling for the generic version of Zosyn approved by FDA violates the plain terms of the statute. Although a statutory exception exists for labeling differences that result from having a new manufacturer, *see* 21 C.F.R. § 314.94(a)(8)(iv), that exception does not and cannot permit labeling differences such as these, which result not from a mere difference in the identity of the manufacturer but rather from fundamental differences in how the drug products themselves *may safely be used.* To find that the labeling differences at issue here—which relate to drug-to-drug interactivity and conditions of administration that, if overlooked, may result in drug deactivation—fall under the regulatory exception for labeling differences describing a new manufacturer's formulation would effectively justify any labeling difference associated with a generic drug formulation, no matter how centrally related to safety. This would entirely upend the same-labeling rule and the statutory scheme of which it is a part, whose fundamental purpose is to ensure that generic drugs are the same as, and freely interchangeable with, their branded counterparts.

Finally, in the face of significant evidence that the ingredient and labeling differences create a serious risk of harm to gravely ill patients, FDA declined even to require the generic

manufacturer to implement a risk management plan to mitigate those risks. In doing so, it again ignored the public health risks arising from the likelihood of product confusion and medication error documented in the administrative record. It gave no explanation whatsoever for doing so, and indeed no explanation whatsoever for its decision not to impose additional risk management measures that go beyond labeling information, even though FDA clearly had the authority to do so. This is textbook arbitrary and capricious behavior by an administrative agency. It was caused by the very same assumption that produced the other errors in FDA's decision: that if a generic drug is safe if used according to the instructions and warnings in its own package insert, the agency may ignore evidence of significant public health risks caused by the likelihood of product confusion and medication errors arising from material differences with the branded drug.

Accordingly, in its complaint, Wyeth asks this Court to set aside FDA's decision to approve the non-equivalent and non-interchangeable generic version of Zosyn. Further, Wyeth asks this Court to enjoin the Agency from approving any generic version of Zosyn unless the generic drug contains the same inactive ingredients as Zosyn and may be administered in the same manner and is compatible with the same drug products as Zosyn. In the alternative, Wyeth requests that the Court prevent the FDA from permitting any such generic product to enter the healthcare system unless and until the generic manufacturer adopts an appropriate risk management plan to educate healthcare professionals about the differences in the generic drug's administration and compatibility profile. Because Wyeth is likely to succeed on the underlying merits, the balance of hardships tips clearly in its favor, and there is a substantial public interest in ensuring that only freely substitutable generic drugs are allowed on the market to protect patient safety, Wyeth respectfully requests that the Court enter an injunction staying the effectiveness of FDA's action and enjoining any further action on Abbreviated New Drug

Applications ("ANDAs") seeking to market generic versions of Zosyn based on the superseded formulation pending this Court's final review of FDA's action on the merits.

STATEMENT OF FACTS

Wyeth's antibiotic Zosyn. Zosyn is an intravenous antibiotic that is widely used to treat gravely ill patients suffering from septic shock, bacterial infections in cancer patients with compromised immune systems, or nosocomial (hospital-acquired) pneumonia.[1] In many acute and intensive care settings, Zosyn is simultaneously co-administered through a single intravenous line with other products.[2] Central to this case is the fact that Zosyn is compatible for simultaneous co-administration with LRS, a commonly used intravenous solution used for fluid resuscitation. In certain emergency situations, *e.g.*, when a patient is in shock, LRS is used to raise the patient's blood pressure by expanding the patient's fluid volume. Ex.1, Manjari Joshi Letter to FDA (Apr. 1, 2008) ("Joshi Letter"), at 1;[3] Ex. 2, Coleman Rotstein Letter to Wyeth Pharmaceuticals (Dec. 15, 2006) ("Rotstein Letter"), at 2. If the patient is in shock due to sepsis (systemic bacterial infection), Zosyn is used in combination with LRS to treat the patient. Ex. 1, Joshi Letter, at 1; Ex. 2, Rotstein Letter, at 2.

The compatibility of Zosyn with LRS has significant clinical advantages. Simultaneous co-administration allows both fluid resuscitation and antibiotic treatment to be delivered to critically ill patients with extra speed. Simultaneous administration also reduces the need for additional vascular drug access sites (reducing the risk of further infection) and reduces the amount of fluid administered to the patient (thereby reducing the risk of congestive heart failure).

---

[1] Zosyn is available in several forms of packaging: (1) single dose vials; (2) pharmacy bulk vials; and (3) Galaxy® containers. Zosyn Galaxy® containers are available as 2.25 g per 50 mL, 3.375 g per 50 mL, and 4.5 g per 100 mL.

[2] Zosyn is prepared and administered by reconstituting and further diluting the drug product in any number of approved diluents and injecting the reconstituted drug product intravenously into the patient. Declaration of David Wu ("Wu Declaration"), at ¶ 5 n.1.

[3] All citations to "Ex." are citations to exhibits attached to the Declaration of Bradford A. Berenson in Support of Plaintiff's Motion for a Temporary Restraining Order and/or Preliminary Injunction.

Wu Declaration, at ¶ 16; Ex. 2, Rotstein Letter, at 1. In patients suffering from shock, simultaneous administration of Zosyn with LRS also prevents the need for sequential administration of the two drug products, which risks loss of blood pressure during the time in which only Zosyn is administered. Declaration of Dr. Manjari Joshi ("Joshi Declaration"), at ¶ 13. Because patients suffering from shock cannot tolerate even temporary drops in blood pressure, the ability to continuously and simultaneously resuscitate the patient with LRS while treating the underlying bacterial infection provides significant treatment advantages that improve clinical outcomes. *Id.*

The original formulation of Zosyn. The original formulation of Zosyn obtained FDA approval in 1993. Wu Declaration, at ¶ 18. Unlike the current formulation, the original was incompatible with LRS.[4] *Id.*; Ex. 3, Wyeth Citizen Petition, at 2, 10-12. When mixed with LRS, the active ingredient piperacillin sodium in the original formulation of Zosyn was deactivated. Deactivation of a necessary antibiotic in a critically ill patient is obviously a matter of grave concern. Accordingly, the labeling for the original formulation included the following capitalized and bolded warning:

"**LACTATED RINGER'S SOLUTION IS NOT COMPATIBLE WITH ZOSYN.**"

Ex. 4, Sandoz Citizen Petition, Appendix A, at 21.

The reformulated version of Zosyn. Wyeth no longer manufactures, markets, or sells the original formulation of Zosyn. Wu Declaration, at ¶¶ 39-40; Wyeth Citizen Petition, at 14. Several years ago, it was superseded by a reformulated version. Wu Declaration, at ¶ 37; Wyeth Citizen Petition, at 14. That reformulation occurred as a result of a tightening of certain

[4] It was also incompatible with certain antibiotics of the aminoglycoside class, such as amikacin and gentamicin. Ex. 3, Wyeth Citizen Petition (Apr. 25, 2006) ("Wyeth Citizen Petition"), at 2, 10-12. Accordingly, the labeling for the original formulation of Zosyn warned against mixing it with these drugs. Ex. 4, Sandoz Citizen Petition (Nov. 1, 2005) ("Sandoz Citizen Petition"), Appendix A, at 12. The reformulated version is compatible with these drugs.

compendial standards the original formulation could not consistently meet. It also had the effect of significantly improving the compatibility profile of the drug, including by rendering it compatible with LRS.

As a parenteral drug, Zosyn is injected directly into the patient's bloodstream. Many injectable products, such as Zosyn, inevitably contain very small amounts of subvisible particulate matter (*i.e.*, contaminants). Excessive levels of particulate matter pose a risk of adverse health effects, including injection-site irritation, phlebitis (*i.e.*, inflammation of the veins), respiratory distress, and even death. Ex. 3, Wyeth Citizen Petition, at 3-4; Ex. 5, Robert Kuhn Letter to FDA (April 3, 2008) ("Kuhn Letter"), at 1; Ex. 24, Lance Peterson and Mira Suseno Letter to FDA (Jan. 10, 2007).

Given the concerns raised by excessive particulate levels, FDA requires injectable drugs to meet the USP standard for particulate matter.[5] Wu Declaration, ¶ 21; *see also* Ex. 6, Nath et al., Pharmacopeial Forum 30:2272 (2004). The USP is recognized by the FDCA as the official standards-setting authority for all prescription products manufactured and sold in the United States. *See* 21 U.S.C. § 321(g)(1) (the term "drug" includes "articles recognized in the official United States Pharmacopoeia").

The original formulation of Zosyn satisfied the USP standard for particulates when it was approved in 1993. Wu Declaration, at ¶ 22; Ex. 3, Wyeth Citizen Petition, at 4. In 1995, however, the USP standard for particulates was tightened. *Id.* In 2000, unexpected levels of particulate matter were found in certain batches of the original Zosyn formulation. Wu Declaration, at ¶ 24; Ex. 7, Geoffrey Levitt Letter to FDA (Jan. 20, 2006) ("1/20/06 Levitt Letter"), at 3. Although these batches generally met the 1993 USP standard for particulates, they did not meet the more stringent standard established in 1995. Wu Declaration, at ¶ 24. When

[5] The USP standard for particulate matter in injectable drugs is USP General Chapter <788> ("USP <788>").

these results were reported to FDA, the Agency expressed concern about these findings. *Id.*; 1/20/06 Levitt Letter, at 3. With experimentation, Wyeth discovered that changes in the inactive ingredients of the original Zosyn formulation provided a robust solution that prevented high levels of particulate formation with all approved diluents. The changes consisted of the addition of a buffer, citric acid, to control the pH and a metal-ion chelator, EDTA, to remove metal-ions from the diluents. Wyeth Citizen Petition, at 8; Wu Declaration, at ¶¶ 29-33.

In addition to resolving the particulate issue, this change to the chemical composition of Zosyn also had other significant therapeutic benefits. Of principal relevance here, unlike the original formulation, the reformulated version of Zosyn could be simultaneously co-administered with LRS without drug deactivation. Wu Declaration, at ¶ 34; Ex. 7, 1/20/06 Levitt Letter, at 5-6; Wyeth Citizen Petition, at 2, 10. The compatibility of reformulated Zosyn with LRS is a direct result of the addition of EDTA and citric acid to the drug formulation. Wu Declaration, at ¶ 35; Wyeth Citizen Petition, at 10.

In May 2005, Wyeth sought FDA approval to market the reformulated version of Zosyn. Wu Declaration, at ¶ 35; Ex. 7, 1/20/06 Levitt Letter, at 5. Wyeth also obtained a patent on the reformulated version. In conjunction with Wyeth's supplemental NDA, Wyeth revised the product labeling to reflect the new compatibility profile. Among other changes, the labeling for reformulated Zosyn removes the capitalized and bolded warning against use with LRS and states that the product is compatible with LRS. Ex. 8, FDA Approved Labeling for Zosyn, at 23. On September 30, 2005, FDA approved reformulated Zosyn with the revised labeling. Wu Declaration, at ¶ 37; Ex. 7, 1/20/06 Levitt Letter, at 5.

Upon approval of the reformulated version of Zosyn, Wyeth immediately began phasing out its original formulation of Zosyn by introducing and marketing the reformulated version with

the new FDA-approved labeling. Wu Declaration, at ¶¶ 38-39; Ex. 7, 1/20/06 Levitt Letter, at 13-14; Ex. 3, Wyeth Citizen Petition, at 14-15. To ensure that the new information would reach as many doctors, nurses, pharmacists, and other healthcare professionals as possible, and to avoid any product confusion or medication error during the transition period, Wyeth initiated an extensive program to educate the medical community about reformulated Zosyn and its differences with the original formulation. Wu Declaration, at ¶¶ 38-39. At the present time, only the reformulated version is marketed by Wyeth. Wu Declaration, at ¶ 40.

Healthcare professionals rapidly changed their patient care practices to take advantage of the enhanced drug compatibility profile of reformulated Zosyn. Based on third party data, Wyeth believes that, in 2006, Zosyn was concomitantly administered with LRS in approximately 104,832 patients. Declaration of William Friedrich ("Friedrich Declaration"), at ¶ 16; Ex. 20, Geoff Levitt Letter to FDA (Jun. 8, 2007) ("6/8/07 Levitt Letter"), at 6. Nearly half (43%) of patients who received Zosyn with LRS received them simultaneously. Friedrich Declaration, at ¶ 16; Wu Declaration, at ¶ 17; Ex. 20, 6/8/07 Levitt Letter, at 6. Those numbers are likely to have increased during the past several years; but at a minimum, based upon the 2006 data, it is safe to say that tens of thousands of critically ill patients each year currently receive Zosyn and LRS through simultaneous intravenous co-administration.

The Hatch-Waxman regulatory regime. Under the FDCA, a drug maker seeking to market a new drug must submit a New Drug Application ("NDA") for the drug, as Wyeth did in the case of its original formulation of Zosyn.[6] *See* 21 U.S.C. §§ 355(a), (b).

In 1984, Congress passed the Hatch-Waxman Act, which amended the FDCA by establishing a streamlined process for the approval of generic versions of brand name drugs. *See*

[6] Wyeth initially filed an antibiotic application under Section 507 of the FDCA. In 1997, Section 507 was repealed, and approved antibiotic applications were deemed to be approved NDAs. 21 U.S.C. § 357 (repealed 1997).

Pub. L. No. 98-417, 98 Stat. 1585 (codified, in part, at 21 U.S.C. § 355(j)). Under the Hatch-Waxman Act, the maker of a generic copy of a listed innovator drug is not required to invest in human clinical trials to prove safety and efficacy. Rather, a generic drug maker may submit an ANDA that relies on the findings of safety and effectiveness for the innovator product, otherwise known as the "Reference Listed Drug." *See* H.R. Rep. No. 98-857(1), at 16 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647; *see also In re Barr Labs., Inc.*, 930 F.2d 72, 73 (D.C. Cir. 1991) (ANDA process "permits generic drug applications to piggy-back on clinical findings that FDA has already embraced" in the NDA).

The crux of the bargain embodied by the Hatch-Waxman Act, however, is that the advantages of this abbreviated process are available only if the generic drug maker can demonstrate that its drug is the same as the Reference Listed Drug in all relevant respects. *Id.* As the main House Report clearly stated, "[T]he focus of the [amendments] is to provide the Food and Drug Administration with sufficient information to assure that the generic drug is the same as the listed drug." H.R. Rep. No. 98-857(1), at 21. Given that the generic drug relies on the finding of safety and efficacy for the innovator drug, Congress and FDA recognized that material differences between the products undermine the conclusion that the generic drug is as safe and effective as the pioneer drug. *See* Abbreviated New Drug Application Regulations (Final Rule), 57 Fed. Reg. 17950, 17961 (April, 28 1992) (codified at 21 C.F.R. pts. 2, 5, 10, 310, 314, 320, 433). Accordingly, the Hatch-Waxman Act requires a generic drug to be identical to the listed drug with respect to, *inter alia*, the active ingredient, the route of administration, the dosage form, the strength of the drug, and labeling, with limited exceptions.[7] 21 U.S.C. § 355(j).

[7] The Hatch-Waxman Act authorizes an ANDA applicant to submit an ANDA, pursuant to an approved suitability petition, for a generic drug that differs from the listed drug in certain respects. *See* 21 U.S.C. § 355(j)(2)(A), (C); 21 C.F.R. § 314.93. The approval of generic Zosyn at issue here was not made pursuant to a suitability petition.

Generic Zosyn based upon the original formulation. On November 1, 2005, shortly after FDA approved Wyeth's reformulated version of Zosyn, Sandoz Inc. ("Sandoz") submitted a request to FDA for permission to submit an ANDA for approval to market a generic version of Zosyn. This application was based on the discontinued formulation and, in pertinent part, the old labeling for Zosyn, including the capitalized and bolded warning against co-administration with LRS. Ex. 4, Sandoz Citizen Petition. After Sandoz filed its request, several other generic drug companies, including Orchid Healthcare ("Orchid"), also sought approval to market generic versions of Zosyn based on Wyeth's superseded formulation and labeling.[8]

In light of the safety and legal issues raised by the differences between the proposed generic versions of Zosyn and Zosyn, Wyeth timely filed comments in opposition to these requests. *See, e.g.* Ex. 7, 1/20/06 Levitt Letter. Wyeth also filed a citizen petition asking FDA not to approve any ANDAs for a generic version of Zosyn unless the proposed generic drug was shown to meet two conditions. First, Wyeth asked FDA to require that the generic drug comply with the current USP standard for particulate matter when used with each of the diluents listed on the product labeling, as does reformulated Zosyn. Ex. 3, Wyeth Citizen Petition, at 1. Second, Wyeth asked that FDA require the generic drug maker to establish that generic Zosyn has the same drug compatibility profile as reformulated Zosyn. *Id.*

Wyeth noted that differences in drug interactivity between a generic drug and its branded counterpart could pose serious risks if healthcare workers either were unaware of those differences or, even if aware, were confused about which form of the drug they were using.

[8] Requests were also submitted by Abraxis Pharmaceutical, and the law firm of Rakoczy Molino Mazzochi Siwik LLP on behalf of an unidentified client. Ex. 9, Abraxis Letter to FDA (Apr. 27, 2006) ("Abraxis Letter"); Ex. 10, Orchid Citizen Petition (Oct. 23, 2006) ("Orchid Citizen Petition"); Ex. 11, Rakoczy Letter to FDA (May 9, 2006) ("Rakoczy Letter").

Wyeth Citizen Petition, at 11-12. If generic Zosyn were erroneously reconstituted with LRS, it could deactivate the antibiotic and potentially result in serious harm to the patient. *Id.* at 12.

As Wyeth pointed out, the risk of error would not be meaningfully mitigated by the generic drug makers' use of the original Zosyn labeling disclosures concerning drug interactions. *See id.* Healthcare professionals justifiably rely on the fact that the Hatch-Waxman Act requires generic drugs to be the same as their branded counterparts in all material respects and assume, as intended by Congress, that a generic product is freely interchangeable with the brand name drug and that it bears the same labeling as its branded counterpart. Accordingly, they have no reason to scrutinize the labeling for any differences and, as a matter of clinical practice, rarely do so. That is especially so in acute and critical care settings such as emergency rooms, where Zosyn is often co-administered simultaneously with LRS. Moreover, even if the differences were understood, many physicians have privileges at multiple healthcare facilities, who may have different versions of Zosyn on their approved formularies. This could lead to confusion and significant medication errors. *Id.* at 11.

Wyeth asked in the alternative that, if FDA were to approve a generic substitute for Zosyn that did not have the same compatibility as Zosyn with LRS, such approval be conditioned on the generic sponsor implementing a risk minimization action plan designed to (1) educate the medical community that the generic form was different from the branded form of Zosyn, (2) minimize the risk of confusion, and (3) prevent adverse health consequences. Ex. 3, Wyeth Citizen Petition, at 2, 13. Wyeth's suggestions were based on the types of measures that Wyeth itself had employed to minimize risk during the transition period when both the original formulation of Zosyn and the reformulated version of Zosyn were present in hospitals and the drug distribution channels. *Id.* at 14-15.

Prominent members of the medical community submitted comments opposing approval of nonequivalent generic versions of Zosyn due to the risk of confusion and medication errors. These commenters included one of the world's leading experts on medication errors, Dr. J. Lyle Bootman, Dean of the College of Pharmacy at the University of Arizona and co-chair of the Committee on Identifying and Preventing Medication Errors of the National Academy of Sciences' Institute of Medicine ("IOM").[9] Ex. 12, J. Lyle Bootman Letter to FDA, (Mar. 26, 2007) ("Bootman Letter"), at 1. During Dr. Bootman's tenure as co-chair of the IOM, the Committee issued a comprehensive report titled "Preventing Medication Errors," which was commissioned by defendant U.S. Department of Health and Human Services to provide recommendations to, among others, defendant FDA regarding how to prevent medication errors.[10] *Id.* Dr. Bootman concluded that there was a significant risk of medication error arising from the concurrent marketing of reformulated Zosyn and one or more generic products based on the discontinued formulation. *Id.* at 2; *see also* Declaration of J. Lyle Bootman ("Bootman Declaration"), at ¶¶ 17-35. Recognizing that the generic labeling would include warnings against inappropriate co-administration, Dr. Bootman nonetheless commented:

> In my view, this reliance on detail buried in the lengthy product prescribing information is *exactly the sort of labeling problem that leads to medication errors.* While hospital personnel may make a good faith effort to use each version appropriately, it seems inevitable that mistakes will occur. The generic version is likely to be used when it is not appropriate to do so, potentially resulting in harm to patients.

[9] The IOM is a component of the National Academy of Sciences, which was created by the Federal government to be the nation's advisor on scientific and technological matters.

[10] Preventing Medication Errors, Committee on Identifying and Preventing Medication Errors, Institute of Medicine, National Academy of Sciences, (July 20, 2006).

Ex. 12, Bootman Letter, at 2 (emphasis added). Therefore, Dr. Bootman concluded that the "concurrent availability of non-interchangeable forms of the same drug poses a risk to the public health due to the drugs' different drug interactivity profiles." *Id.*

Dr. Manjari Joshi of the University of Maryland R. Adams Cowley Shock Trauma Center also submitted comments to FDA warning about the significant risk of medication errors:

> Having practiced medicine for over 25 years, I have learned that physicians and nurses generally expect generic drugs to be equivalent to, and freely interchangeable with, their branded counterparts. Should a generic version of piperacilin-tazobactam be marketed that is not compatible with Lactated Ringer's solution..., there is a serious and real risk that this antibiotic drug will be used in situations that are improper, i.e., where compatibility with Lactated Ringer's solution...is mistakenly believed to exist because of prior experience with the branded counter drug product.

Ex. 1, Joshi Letter, at 2 (emphasis added); *see also* Ex. 13, Steven Ebert Letter to FDA (Sept. 7, 2006) ("Ebert Letter"), at 2 ("[c]onfusion in a hospital pharmacy can easily lead to medication errors, which in this case would result in very ill patients receiving inactivated antibiotic....").

In response, the generic drug companies principally argued that, since Wyeth's original formulation of Zosyn was approved as safe and effective, a generic substitute based on that formulation posed no safety or effectiveness risk.[11] The issue identified by Wyeth, however, was not the safety or effectiveness of the old formulation *per se*, but rather the risks to safety and effectiveness resulting from the *concurrent marketing* of Zosyn and Zosyn substitutes that are different in their drug compatibility profile and cannot safely be administered under the same accepted conditions of use. Ex. 7, 1/20/06 Levitt Letter, at 9; Ex. 3, Wyeth Citizen Petition, at 11. To the extent the generic drug makers addressed those risks at all, they contended merely that the labeling they proposed to use (the original labeling used by Wyeth) adequately disclosed

[11] Ex. 9, Abraxis Letter at 3; Ex. 10, Orchid Citizen Petition, at 2; Ex. 11, Rakoczy Letter, at 3-4.

such risks and would prevent any confusion or harm.[12] No generic drug maker provided any evidence to support that contention or to refute the contrary views filed by the experts from the medical and pharmacy fields who supported Wyeth. The administrative record is essentially uncontradicted on this central point.

FDA's decision to approve generic Zosyn. [13] Nonetheless, on September 15, 2009, in a consolidated response, FDA granted the citizen petitions filed by the generic drug manufacturers and denied in part and granted in part Wyeth's citizen petition. FDA simultaneously approved the ANDA submitted by Orchid, one of the generic drug companies that filed a citizen petition seeking approval to market a generic formulation of Zosyn based on Wyeth's superseded formulation and labeling. Immediately thereafter, Orchid's generic product was listed as a "therapeutic equivalent" to Wyeth's reformulated version of Zosyn in FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the "Orange Book." *See* Ex 14 (excerpts from paper and electronic versions).

FDA essentially adopted the position urged by the generic drugmakers wholesale, justifying every step in a serpentine course of dodging the statutory and regulatory requirements of sameness by reference to the intrinsic safety of the original formulation and the original labeling as approved sixteen years earlier, without regard to the vastly changed circumstances occasioned by the widespread use of the reformulated version. Apart from a talisman faith in differential labeling, whose lack of practical effect was the precise issue raised by Wyeth, FDA made no effort to address the risks to patient safety documented in the administrative record.

---

[12] Ex. 9, Abraxis Letter, at 3; Ex. 10, Orchid Citizen Petition, at 3; Ex. 11, Rakoczy Letter, at 8, 11.

[13] This section describes FDA's ruling in pertinent part. The decision contains additional findings that are not directly relevant to the present motion. For example, the Agency represented that, like Wyeth's reformulated version of Zosyn, Orchid's generic product is compatible with the aminoglycosides amikacin and gentamicin, and that Orchid's generic product will be required to comply with existing USP standards limiting particulate levels in parenteral drugs. Based on these representations, Wyeth does not address herein the potential safety and efficacy and legal issues that would be raised by a generic that does not exhibit these characteristics but reserves the right to do so if the evidence in this case or later approvals of other ANDAs so warrant.

FDA's decision acknowledges that Orchid's generic Zosyn formulation uses the older, superseded formulation of Zosyn and that it therefore does not contain the inactive ingredients EDTA and citric acid. Ex. 15, September 15, 2009 Letter from Janet Woodcock, Director, CDER, to Beth Brannan et al. ("FDA Decision"), at 5. It further admits that the approved generic formulation exhibits a different drug compatibility profile as compared to Wyeth's Zosyn product—in particular, that the generic formulation is not compatible with LRS. *Id.* at 6. FDA further acknowledges that the incompatibility of the approved generic formulation with LRS means that if they were simultaneously co-administered (in the manner in which tens of thousands of patients now receive the reformulated version of Zosyn each year), the piperacillin sodium active ingredient in Zosyn would be deactivated. *Id.* at 16 (stating that mixing will result in an "inactive lactate-piperacillin adduct"). In other words, if the errors the experts have warned FDA about occur, gravely ill patients in life-threatening situations will potentially not receive effective antibiotic treatments ordered by their doctors. According to FDA, Orchid's own studies demonstrate that the presence of EDTA and citric acid in Wyeth's reformulated version of Zosyn inhibits this drug deactivation. *Id.* FDA also acknowledged that EDTA and citric acid play a role in preventing particulate formation in Zosyn. *Id.* at 9.

Notwithstanding its recognition that EDTA and citric acid play a role in reducing particulates and prevent LRS from deactivating the antibiotic in Zosyn, the Agency determined that it could approve a generic without these two inactive ingredients. According to FDA, citric acid fell under the exception for differences in buffers in parenteral drug products that do "not affect the safety or effectiveness of the proposed product." *Id.* at p. 11 (citing 21 C.F.R. §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B)). With respect to EDTA, FDA recognized that EDTA was not a buffer, preservative, or antioxidant, and that it therefore did not fall under any

recognized exception to the requirement for identity in inactive ingredients. FDA Decision, at 11. FDA therefore simply waived the regulatory sameness requirement for this inactive ingredient in order to approve the generic. FDA did so because it found that the superseded formulation of Zosyn was intrinsically safe and effective if used in accordance with the old labeling, just as was the old formulation during the time it was marketed. *Id.* According to FDA, "[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. FDA never addressed the risk of patient harm arising from the likelihood of confusion and medication error arising from having *two different* formulations of Zosyn on the market that cannot safely be used in the same way. It never addressed the changed circumstances created by the existence of the reformulated version at all. Instead, even though that issue was central to Wyeth's Citizen Petition and was the subject of considerable comment and record evidence, FDA simply ignored it.

FDA also looked past the fact that the generic has materially different labeling than its branded counterpart; indeed, it used the differential labeling to justify its decision approving differential ingredients. Given that the approved generic formulation is not compatible with LRS, the approved labeling for the generic product includes the same warning against co-administration with LRS that was in the labeling for the old formulation. *Id.* at 5, 13. No such warning is included in the labeling for Wyeth's reformulated Zosyn. The Agency nonetheless found that the generic complied with the statutory requirement that the labeling for the generic be the "same" as the branded drug. 21 U.S.C. § 355(j)(2)(A)(v). It did so by shoehorning the

LRS incompatibility warning into a narrow statutory exception "for changes required ... because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). An FDA regulation describes allowable differences under this exception as including differences in "formulation" that result from having a different manufacturer. 21 C.F.R. § 314.94(a)(8)(iv). Despite the fact that the labeling difference here relates to safety, compatibility, and method of administration, and in no way describes a difference in formulation, FDA appears to have read this regulation to mean that a generic drug labeling can vary from the approved labeling for the Reference Listed Drug in any way necessary to take account of the *effects* of a difference in formulation, as long as the generic was manufactured by a different company. As the Agency summarized its reasoning, "Orchid's generic [product] is permitted to have different labeling than reformulated Zosyn to account for differences in formulation because the product is produced or distributed by a different manufacturer." *Id.* at 16. According to this reading of the statute, every labeling difference in a generic product, no matter how central to safety, is essentially self-justifying.

As it did in casting aside the same-inactive-ingredients requirement, the FDA ignored the broader public health implications of its interpretation of the manufacturer exception to the same-labeling requirement. FDA's decision gave no meaningful consideration to the risk of medication error and confusion raised by the concurrent marketing of a generic formulation of Zosyn whose labeling warns against a method of administration used tens of thousands of times each year with the branded version currently on the market. Despite substantial evidence to the contrary, the Agency decision simply assumed that warnings provided in the generic labeling will be adequate "to assure the safe use of the drug." *Id.* at 11; *see also id.* at 16 ("Orchid's generic ... labeling informs health care providers about the incompatibility of Orchid's product

with LRS, such that the product will be safe and effective under the labeled conditions of use." That is of course the precise question at issue, and the Agency almost entirely begs it. Except for stating that the "few letters from health care providers submitted by Wyeth are speculative and conclusory in nature" (*id.* at 17 n.38)—itself a conclusory finding—the Agency simply ignores the substantial evidence in the administrative record indicating that warnings in labels will be inadequate given the universal expectation that generic drug products are the same as, and interchangeable with, their branded counterparts.

Finally, the Agency determined that a risk management plan was not necessary for the approved generic formulation. *Id.* at 17. Here, the FDA made literally no attempt to provide a reasoned explanation for its decision. The Agency was presented with powerful evidence of risks caused by having two different products on the market that healthcare professionals would likely believe were the same. Among other things, the Agency received a detailed submission by Dr. J. Lyle Bootman, the Co-Chair of the Committee on Identifying and Preventing Medication Errors of the National Academy of Sciences' Institute of Medicine and one of the world's leading experts on medication errors. Yet in two short paragraphs, the FDA merely summarized Wyeth's request, stated that it "disagree[d]" with it, reiterated its prior irrelevant conclusion that the generic was intrinsically safe and effective and its question-begging assumption that the generic formulation "has appropriate labeling that adequately informs health care providers about the compatibility of the product to ensure safety and effectiveness of the product," and stated without explanation or justification in light of the record evidence that "the Agency has concluded that no additional steps are necessary to alert health care practitioners of the differences" between the Orchid generic and the Wyeth branded products. *Id.*

ARGUMENT

A party is entitled to injunctive relief if (1) it has a substantial likelihood of success on the merits of the underlying case; (2) it will be irreparably injured if an injunction is not granted; (3) other interested parties will not suffer substantial harm if preliminary relief is granted; and (4) the public interest will be furthered by the injunction. *Nat'l Treasury Employees Union v. United States*, 927 F.2d 1253, 1254 (D.C. Cir. 1991); *Cobell v. Norton*, 391 F.3d 251, 258 (D.C. Cir. 2004). The factors supporting an injunction "should be balanced on a sliding scale, and a party can compensate for a lesser showing on one factor by making a very strong showing on another factor." *Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 159 (D.D.C. 2006). Wyeth is entitled to relief because all the relevant factors strongly favor an injunction.

I. WYETH IS LIKELY TO SUCCEED ON THE MERITS.

The FDA's approval of Orchid's generic formulation of Zosyn is arbitrary, capricious, and contrary to law. Contrary to its statutory mandate, its own regulations, and the evidence in the administrative record, the Agency approved a generic formulation of Zosyn that is so different from the branded drug that it cannot safely be used in the same way. The FDA has utterly failed to justify this unprecedented decision.

A. FDA's Approval Of Orchid's Generic Zosyn Product Violates The Same Ingredients Requirement.

The Hatch-Waxman Act generally requires that the generic drug have the same active ingredients as the innovator drug. 21 U.S.C. §§ 355(j)(2)(A)(ii)(I); 21 C.F.R. § 314.94(a)(9)(iii). In the case of parenteral drugs (*i.e.*, drugs administered by injection, such as Zosyn), FDA has imposed heightened sameness requirements to ensure patient safety. 54 Fed. Reg. at 28883. With respect to inactive ingredients, FDA's regulations require that, absent a waiver, a generic parenteral drug have the same inactive ingredients as the innovator drug, and in the same

concentrations. 21 C.F.R. §§ 314.94(a)(9)(iii), 314.127(a)(8)(ii)(B). The Agency has explained that generic parenteral drugs should generally have the "identical" formulation as the innovator drug because (as this case itself amply demonstrates) parenteral formulations are especially sensitive to changes in inactive ingredients. 54 Fed. Reg. at 28884. Exceptions are made for preservatives, buffers, and antioxidants, but even changes in these categories of inactive ingredients are presumed to jeopardize the safety and effectiveness of the drug, and FDA will refuse to approve an ANDA for a generic that contains different ingredients of these types unless the applicant comes forth with "sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product." 21 C.F.R. §§ 314.127(a)(8)(ii)(B), 314.94(a)(9)(iii); *see also* 54 Fed. Reg. at 28883 ("the agency will presume any inactive ingredient in an applicant's proposed drug product different from that in the reference listed drug to be unsafe unless the applicant can rebut the presumption by demonstrating that the different inactive ingredient will not affect the safety of its . . . product.").

It is undisputed that Orchid's generic version of Zosyn does not have the same inactive ingredients as the branded medication currently in use nationwide. Zosyn contains EDTA as a metal-ion chelator and citric acid as a pH buffer, while the approved generic version does not. Because EDTA functions neither as a "preservative, buffer, or antioxidant," *see* FDA Decision, at 11, it must be included in the generic formulation of Zosyn under the FDA's own regulations, absent a waiver. 21 C.F.R. § § 314.94(a)(9)(iii), 314.127(a)(8)(ii). In addition, although citric acid functions as a buffer, Orchid did not furnish sufficient information to rebut the presumption that a generic product without it would not be safe for use. Nor could it, given the undisputed evidence of the role that EDTA and citric acid play in preventing the formation of particulates as well as drug deactivation when Zosyn is mixed with LRS, a commonly used fluid resuscitative

agent with which Zosyn is routinely co-administered.[14] Thus, citric acid should also have been required to be included in the generic formulation of Zosyn under FDA's own regulations. 21 C.F.R. § 314.127(a)(8)(ii)(B).

FDA based its approval of a generic formulation missing these two inactive ingredients upon a finding that the absence of citric acid satisfied the regulatory safety test for excusing a difference in buffers, and waiving entirely for EDTA the flat regulatory prohibition on differences in inactive ingredients other than buffers, preservatives, and antioxidants. FDA Decision, at 11-12. FDA justified both of these conclusions on the grounds that the Agency had previously found the original formulation of Zosyn, on which the generic is based, to be safe and effective, and that the differences between the generic version of Zosyn and reformulated Zosyn would be disclosed in the labeling for the generic product. *Id.* In essence, the FDA found that because the old formulation of Zosyn was safe when it was approved sixteen years ago, it continues to be safe. It then used that finding of intrinsic safety to justify the regulatory safety finding and waiver on citric acid and the waiver on EDTA.

This reasoning completely misses the point. The heart of the problem presented to the Agency is not based on the circumstances that existed sixteen years ago, but rather on the situation at hand now: the danger that reintroduction into the marketplace of a generic based upon a superseded formulation with a different compatibility profile than the currently marketed innovator drug presents undue risks of confusion and medication error. Ex. 12, Bootman Letter,

---

[14] The Agency states that "assuming arguendo that [the approved generic formulation of Zosyn] is inadvertently diluted with LRS, the available evidence does not indicate there would be adverse effects." FDA Decision, at 16. To the contrary, as FDA itself acknowledges, mixing of these incompatible drug products will result in "a biologically inactive lactate-piperacillin adduct," *i.e.*, deactivation of the piperacillin sodium component of Zosyn. *Id.* According to FDA's regulations, "any failure of expected pharmacological action" is defined as an "adverse event." 21 C.F.R. § 314.80(a). Such adverse events can be devastating when they involve injectable drugs and LRS. For example, several neonatal deaths were recently linked to particulates found in Rocephin® (ceftriaxone) as a result of the incompatibility of that injectable drug with LRS. *See* FDA Alert, Information for Healthcare Professionals: Ceftriaxone (marketed as Rocephin) (Sept. 11, 2007), *available at* <www.fda.gov/cder /drug/InfoSheets/HCP/ceftriaxone.htm>.