**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

| | |
|---|---|
| WYETH PHARMACEUTICALS,<br><br>Plaintiff,<br><br>v.<br><br>U.S. FOOD AND DRUG ADMINISTRATION, *et al.*,<br><br>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>.

at 2; Ex. 1, Joshi Letter, at 2; Ex. 13, Ebert Letter, at 2; Bootman Declaration, at ¶¶ 17-35; Joshi Declaration, at ¶¶ 8-24. The Agency looked only to the intrinsic safety of an old drug under old labeling language and refused to consider safety issues more broadly, in light of subsequent experience, changed circumstances, and the very different legal regime that applies to the introduction of generics alongside branded reference drugs. The Agency's reasoning is manifestly inadequate in light of its past and present policies, the Hatch-Waxman legal regime, and the record of serious risks to patient health before the Agency.

Most fundamentally, FDA's reliance on the original approval of the superseded formulation to find that the similar counterpart generic is acceptable for Hatch-Waxman purposes was based on an impermissibly narrow view of generic drug safety, which focused only on the intrinsic safety of the product under the originally labeled conditions of use and ignored the risks of confusion and error that could result in the product being used in a manner contrary to the labeled warnings. Given the evident purpose of the Hatch-Waxman Act and the related body of law governing generic approvals, statutory and regulatory requirements that generic products be the "same" as their branded counterparts can properly be waived only where the evidence demonstrates not only that differences do not undermine the intrinsic safety of the generic product viewed in isolation, but also that they will not compromise patient health and safety under the prevailing conditions under which the generic product might be substituted for its branded reference product.[15]

FDA's decision is therefore inconsistent with the basic structure and purpose of the Hatch-Waxman Act, which is premised on the idea that generic drugs will be the same as their

[15] Even if, as FDA suggests, the requirement for identity in inactive ingredient was not intended to address the precise situation involved here, *see* FDA Decision, at 11 n.22, that is no reason for ignoring the safety risks presented by waiving the rule in this case, a course of action inconsistent with the FDA's mandate to protect the public health.

branded counterparts and can be used interchangeably with them. Rather than evaluating generic safety in isolation, the entire Act is built upon a foundation of *comparative evaluation* in which the proposed generic is compared with a branded Reference Listed Drug, and a determination of safety is made based precisely on the identity of one product with the other. H.R. Rep. No. 98-857(I), at 21 ("[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.") (emphasis added). To ignore potential safety problems that might be caused by material differences between the two is to abdicate responsibility for the very issue that lies at the heart of the Hatch-Waxman regime. 57 Fed. Reg. at 17961 (recognizing the need to maintain "consistent labeling to assure health professionals and consumers that a generic drug is as safe and effective as its brand-name counterpart"). Under that regime, the whole question before the Agency is whether to allow a generic to be introduced into the market alongside an innovator, not whether the generic drug is intrinsically safe in isolation. For the FDA to avert its eyes from that issue and exclude from consideration new safety problems that might be created by differences between the generic and the Reference Listed Drug is the height of irrationality and administrative arbitrariness. *Motor Vehicle. Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983) (agency action is arbitrary and capricious where it "entirely fail[s] to consider an important aspect of the problem").

Relatedly, FDA's action fails to take account of changed circumstances. *State Farm*, 463 U.S. at 43 (agency must demonstrate a "rational connection between the facts found and the choice made"). Since the approval of Wyeth's original Zosyn formulation, new facts relevant to its safe and effective use have come to light—that is, FDA's approval of Wyeth's reformulated version of Zosyn that exhibits a different drug compatibility profile. Unlike the situation in

1993, another Zosyn formulation is already on the market that can be safely used in an important way that the new generic entrant cannot. The Agency was presented with evidence that this change in circumstance is highly significant, because approval of the generic now makes medication errors and patient harm nearly inevitable. Ex. 12, Bootman Letter, at 1; Ex. 1, Joshi Letter, at 2; Ex. 13, Ebert Letter, at 2; Ex. 2, Rotstein Letter, at 1. FDA's failure to recognize this significant change in circumstance, and to evaluate the generic's safety in light of it, was arbitrary and capricious.

FDA's decision to ignore broader safety issues was also arbitrary and capricious in that it required ignoring the substantial evidence in the record documenting the risks associated with this change in circumstance. *Morall v. DEA*, 412 F.3d 165, 180 (D.C. Cir. 2005) (reversing agency decision as arbitrary and capricious because it "entirely ignored" relevant evidence); *PPL Wallingford Energy LLC v. FERC*, 419 F.3d 1194, 1199 (D.C. Cir. 2005) (agency action was arbitrary and capricious because if failed to "respond meaningfully" to petitioner's objections). There was and is no dispute that the absence of EDTA and citric acid in the generic version of Zosyn results in a significantly different drug compatibility profile from the branded version.[16] The Agency was presented with evidence that, in the real-world context of a busy hospital treating seriously ill patients, medical errors and oversights in the dispensing and administration of prescription drugs are inevitable and not uncommon. *See, e.g.*, Ex. 12, Bootman Letter, at 1; *see also* Ex. 1, Joshi Letter, at 2-3; Ex. 13, Ebert Letter, at 1-2; Bootman Declaration, at ¶¶ 17-35; Joshi Declaration, at ¶¶ 8-24. Yet FDA simply disregarded the evidence suggesting that approval of the generic would cause such errors and hurt patients, instead relying on its irrelevant

[16] In a previous case where a waiver was granted that FDA cites to in its decision (*see* FDA Decision, at 12 n.25), the change in inactive ingredients allegedly resulted in additional injection site pain. Ex. 16, FDA's decision letter from S. Galson, Acting Director CDER, to M. Rapp, Ben Venue Labs., Inc. et al, FDA Docket Nos. 2001P-0574 and 2005P-0061 (March 25, 2005). The change in inactive ingredients had no impact on the drug-to-drug compatibility of the generic injectable drug. Nor did the change necessitate safety-related labeling differences. *Id.*

determination that the old formulation of Zosyn was safe and effective when its labeled warnings are followed. *See, e.g.*, FDA Decision, at 5, 9, 11.

Medication errors will likely occur notwithstanding the labeling information found in the approved generic product. Leading experts and practitioners have opined, based on their substantial experience and expertise, that a significant probability of error remains despite the labeling differences. Ex. 1, Joshi Letter, at 2-3; Ex. 12, Bootman Letter, at 2; Ex. 13, Ebert Letter, at 1-2; Bootman Declaration, at ¶¶ 17-35; Joshi Declaration, ¶¶ 8-24. Although FDA disparaged this evidence as "speculative and conclusory in nature," *id.* at 17 n.38, it failed to explain why. FDA is not entitled to ignore such uncontradicted evidence in the record. *See State Farm*, 463 U.S. at 43; *Pearson v. Shalala*, 164 F.3d at 650, 660 (D.C. Cir. 1999).

In fact, the concerns expressed by these professionals are anything but speculative; they are validated by defendants' own statements. For example, Dr. David J. Graham, Associate Director for Science at the FDA's Office of Drug Safety, testified in 2004 before the Senate Finance Committee that: "Physicians don't read the labeling. It's pretty established [they] don't change physician or patient behavior." U.S. Senate Committee on Finance, Hearing on "FDA, Merck and Vioxx: Putting Patient Safety First?," Testimony of David J. Graham, MD, MPH (November 18, 2004). The risk of confusion is especially acute in community hospitals, which are staffed by physicians having privileges in multiple hospitals who might be uncertain or confused about which version of Zosyn is available at each hospital. Bootman Declaration, at ¶ 35; Joshi Declaration, at ¶ 22.

Further, Congress has recognized that drug labeling is often inadequate to communicate to healthcare professionals and patients the risks associated with the use of a drug. With the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress granted FDA the

authority to require drug sponsors to implement "risk evaluation and mitigation strategies" (REMS) if the Agency deems it necessary to ensure safe use of a drug product. 21 U.S.C. § 355-1. Under its REMS authority, FDA can require drug makers to develop "communication plans" that disseminate information regarding the risks presented by a certain drug. *Id.* In granting this power, Congress has recognized that traditional labeling may not always be sufficient to communicate information necessary for safe and effective drug use.

FDA's stubborn reliance on the old formulation's safety under the terms of the old labeling also runs contrary to FDA's own understanding of how generic drug products are used. FDA itself recognizes that healthcare professionals expect generic drugs to be freely interchangeable with their branded counterparts. *See* August 10, 2009 Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William E. Fitzsimmons et al., Docket No. 2007-P-0111, at 15 (recognizing that generic drug products are "expected to be substitutable for its branded counterpart with the full expectation that the substitute product will produce the same clinical effect and safety profile...."). And, by its designation of Orchid's generic product as a therapeutic equivalent to Wyeth's branded product, FDA has recognized that health care professionals will treat patients "with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product." Orange Book, at vii. FDA has further acknowledged that "consistent labeling" is necessary to "avoid differences that might confuse healthcare professionals." 54 Fed. Reg. at 28881.

In sum, in deciding to approve a generic formulation with different ingredients and a different compatibility profile, FDA committed a veritable litany of APA sins: it ignored its statutory mandate; took too narrow a view of the way in which the Hatch-Waxman Act obliges it to consider generic approvals; relied on old findings that had been undermined by changed

circumstances; ignored the record evidence; and indulged assumptions directly contrary to the Agency's own prior pronouncements. For all these reasons, FDA's decision was arbitrary, capricious, and contrary to law, and should be rejected. *See, e.g., State Farm,* 463 U.S. at 43 (1983) ("the agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made'"); *Alpharma, Inc. v. Leavitt*, 460 F.3d 1, 6 (D.C. Cir. 2006); *Pearson*, 164 F.3d at 660 ("It simply will not do for a government agency to declare – without explanation – that a proposed course of private action is not approved. . . . To refuse to define the criteria it is applying is equivalent to simply saying no without explanation."); *County of L.A. v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999) ("Where the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, [the court] must undo its action.").

### B. FDA's Approval Of Generic Zosyn Violates The Same Labeling Requirement.

The Hatch-Waxman Act also requires that the labeling for a generic drug be "the same" as the labeling approved for the listed innovator drug. 21 U.S.C. § 355(j)(2)(A)(v). FDA has emphasized how critical the same-labeling requirement is to the Hatch-Waxman regulatory scheme. In promulgating the same-labeling regulation, FDA observed that "the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval." 57 Fed. Reg. at 17961. According to FDA, "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Id.* In addition, consistent labeling is necessary to prevent confusion. As described by FDA, "[c]onsistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse healthcare

professionals who prescribe and dispense prescription drug products or might create omissions of significant information." 54 Fed. Reg. at 28881.

Contrary to this clear statutory mandate and its own recognition of the important reasons for it, FDA has approved a generic version of Zosyn that has significant labeling differences compared to reformulated Zosyn. In particular, the labeling for the approved generic version of Zosyn includes warnings against simultaneous co-administration with LRS that are not found in the labeling for Wyeth's formulation of Zosyn. *See, e.g.*, FDA Decision, at 13, 16. This labeling difference is significant, because it relates to differences in drug-to-drug interactivity and differences in conditions of administration, *i.e.*, the safety and efficacy of the drug under expected conditions of use. Moreover, according to some of the country's leading experts on medication errors, this labeling difference is bound to cause confusion.[17] Thus, the generic version of Zosyn approved by FDA violates the plain terms and manifest purposes of the same-labeling provision in the Hatch-Waxman Act.

In attempting to avoid this straightforward conclusion, FDA relies exclusively on the statutory exception for labeling changes required "because the new drug and the listed drug are produced to be distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). This narrow exception has no application here. The statutory text contains no hint that it could embrace significant differences in safety or drug-to-drug compatibility warnings. And the legislative history confirms that the manufacturer exception to the same-labeling requirement is limited to minor labeling differences unrelated to safety and efficacy. Specifically, the legislative history indicates that Congress intended a narrow exception that would include technical differences such as those describing "the name and address of the manufacturers,"

[17] In fact, the labeling for the Orchid product is even more likely to cause confusion given that, with instructions for use with certain aminoglycosides (FDA Decision, at 5), its labeling is neither the same as Zosyn's old labeling (which did not include such instructions) nor Zosyn's current label.

"expiration dates," or the "color" of a pill. H.R. Rep. No. 98-857, pt. 1, at 22. Clearly, Congress did not intend for the exception to include labeling differences that affect the way a generic product may safely be used compared to the Reference Listed Drug, the presumed equivalence of which underlies the entire Hatch-Waxman regime. The Agency action, therefore, reflects a construction of the statute that must be invalidated. *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984); *Gen. Dynamics Land Sys. v. Cline*, 540 U.S. 581, 600 (2004) ("Even for an agency able to claim all the authority possible under *Chevron*, deference to its statutory interpretation is called for only when the devices of judicial construction have been tried and found to yield no clear sense of congressional intent.").

FDA's own regulation interpreting the manufacturer exception confirms this reading. FDA emphasizes that its regulation interprets the statutory exception to include, among other things, differences "in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or [other] exclusivity." 21 C.F.R. § 314.94(a)(8)(iv). FDA places its principal reliance on the inclusion of the word "formulation," reasoning that the labeling difference found in the approved generic formulation of Zosyn is permissible under the statutory and regulatory exception because it "account[s] for differences in formulation because the product is produced or distributed by a different manufacturer." FDA Decision, at 16. However, on its face, the labeling difference FDA authorized here does not simply describe a difference in "formulation," as contemplated by the regulation. Instead, it warns of substantive incompatibility between the product and LRS. No reasonable person could possibly read a regulation allowing a "difference[]] between the applicant's proposed labeling and labeling approved for the reference listed drug" to "include [a] difference[] in . . .

formulation" as embracing a warning that "**LACTATED RINGER'S SOLUTION IS NOT COMPATIBLE WITH**" the applicant's drug.

The interpretation FDA offers to justify its construction of the word "formulation" to include this compatibility warning borders on the absurd. Under FDA's reasoning, *any* labeling difference between a generic drug product and the branded drug product that results from an underlying difference in formulation would be acceptable under the statute. Implicit in FDA's argument is the view that this regulation authorizes unlimited labeling differences that in any way relate to any of the listed subjects, as long as those differences are associated with production by a new manufacturer. But if that is what this exception meant, it would clearly be *ultra vires*, because it would swallow the main statutory prohibition on differences in labeling nearly whole. In almost all cases, the entry of a generic into the marketplace will entail production of the drug by a new manufacturer. If that then *ipso facto* permitted any and all differences in labeling relating to such fundamental subjects as the "formulation, bioavailability, or pharmacokinetics" of the drug, the Hatch-Waxman Act's most basic guarantee – that generic drugs will be the same as the innovator drugs on which they are based – would be eviscerated. Instead, this regulation must be interpreted in light of the statutory text it expounds, and the permissible differences in these categories can only be those that, as the statute plainly indicates, lawfully arise directly from a change in manufacturer and do not affect the safety or efficacy of the generic product as compared with the branded version.[18]

[18] For example, in *Bristol-Myers Squibb, Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), the court upheld FDA's approval of a generic product that omitted a specific indication for use. In that case, the omitted indication was statutorily protected by a three-year marketing exclusivity period held by the innovator drug maker. However, doctors could still safely prescribe the generic "off-label" for the same indications as the branded product because there were *no differences* between the generic and branded products themselves. Thus, not only did the labeling difference fall within the exception for the "omission of an indication or other aspect of labeling protected by patent or [other] exclusivity," 21 C.F.R. § 314.94(a)(8)(iv), it also did not impact how the drug could safely be used.

Indeed, FDA itself has recognized that it may not do what it has attempted to do here: make an exception to the same-labeling requirement for important safety-related information. FDA has previously made clear that exceptions will not be permitted when the differences in the generic drug's labeling would affect the safety or efficacy of the generic drug or require new labeled warnings that are not in the labeling of the branded product. As FDA has explained:

> FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions . . . of the act. . . . ***Thus, where a proposed change in a generic drug, e.g., in packaging or inactive ingredients . . . would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings, the proposed product would not satisfy the labeling requirements of . . . the act.***

54 Fed. Reg. at 28884 (emphasis added). When the proposed generic labeling involves "the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened label warnings," FDA has indicated that such labeling would not fall under any exception and would not satisfy the labeling requirements of 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(4)(G). *Id.*

That is precisely the situation presented here. The warnings against co-administration with LRS found in the labeling for Orchid's generic product are "new warnings or precautions" which are "intended to address newly introduced safety or effectiveness problems not presented by the listed drug." 54 Fed. Reg. at 28884. The differences at issue here reflect fundamental differences between the generic Zosyn product and the branded Zosyn product that have important safety implications in the clinical setting. Put simply, the drugs are not clinically equivalent, and the labeling differences indicate that they may not safely be administered in the

same way. Consequently, the Hatch-Waxman Act and its implementing regulations clearly prohibited approval of the Orchid product.

To the extent that the Fourth Circuit decision on which FDA places principal reliance, *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000) ("*Zeneca*"), validated a generic drug approval that required an additional safety warning, that case was incorrectly decided for the same reasons, and it is distinguishable in any event.[19] In *Zeneca*, a generic version of Diprivan®, which is a parenteral product, contained a different preservative than the branded product. *Id.* at 165. Because some people were potentially susceptible to an allergic reaction to the "sulfite" preservative used in the generic (*i.e.*, sodium metabisulfite), a warning was added to the generic labeling. *Id.* at 169. Despite the labeling differences, FDA approved the generic product. However, as discussed above, FDA's regulations under the Hatch-Waxman Act expressly allow the substitution of one preservative for another, and the labeling difference simply accommodated that authorized change in formulation. Further, the new warning found in the generic substitute was *required* under a separate FDA regulation for *all* products containing the sulfite inactive ingredient at issue in that case. *Id.* at 169. That regulation reflected generalized concerns regarding sulfite reactions and notes that "[t]he overall prevalence of sulfite sensitivity in the general population *is unknown and probably low*." 21 C.F.R. § 201.22(b) (emphasis added). Unlike the Diprivan situation and the generic product there, the incompatibility of LRS with the approved generic formulation is undisputed, is not required by another prophylactic regulation, and presents real and nonspeculative risks to patients in acute medical care settings. The manufacturer exception to the Hatch-Waxman Act's same-labeling

[19] The other "precedent" that FDA relies upon is its decision reflected in its April 19, 2005 letter from Randall W. Lutter, Acting Associate Commissioner for Policy and Planning, to Stephen Paul Mahinka and Kathleen M. Sanzo, Docket No. 1999P-1654. FDA Decision, at 16 n.37. That decision involved the same issues as the *Zeneca* decision and is inapposite for the same reasons.

requirement simply cannot accommodate such a change, which goes to the core equivalency and interchangeability required by Congress for generic drug approvals.

### C. FDA's Failure To Explain Why It Refused To Require A Risk Management Plan Was Arbitrary And Capricious.

Even if it were lawful for FDA to approve Orchid's generic formulation of Zosyn, Wyeth urged the FDA to require generic drug makers to safeguard patient health by adopting a risk management program to inform the healthcare community of the differences in administration between the generic versions of Zosyn and Zosyn. Ex. 3, Wyeth Citizen Petition, at 1-2. FDA developed the concept of "RiskMAPs" specifically for use in minimizing known risks of a product while preserving its benefits. FDA Guidance for Industry: Development and Use of Risk Minimization Action Plans, at 5 (Mar. 2005), *available at* <www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf>. FDA recognized that, in addition to warnings on labeling, risks arising from approved drugs may warrant additional measures to ensure patient safety, including targeted education and reminder systems. *Id.* at 7. The Agency practice was essentially codified in the REMS authority given to the Agency by Congress in the FDAAA, as discussed above. 21 U.S.C. § 355-1.

This alternative course would have been more protective of the public health. It would have been consistent with what Wyeth itself did during the brief period of transition from the old to the new formulation of Zosyn. Wu Declaration, ¶¶ 38-40. And it would have been consistent with the decision of the National Health Service in the United Kingdom to require a rigorous program of precautions before any generic Zosyn based on the superseded formulation could be marketed or sold there—a decision made in the context of a single-payer, centrally controlled system where the risk of disuniformity of practice and confusion is far less than in the United States' diverse and diffuse health care delivery system. Ex. 22, Medicines and Healthcare

Product Regulatory Agency: Safety Information Regarding Launch of Generic Medicines that Contain Piperacillin and Tazobactam. Yet the Agency rejected a risk management plan without any serious consideration of its advantages and disadvantages (if any). In so doing, the FDA offered no reasoned explanation for its decision, simply stating in conclusory fashion that it had determined that "no additional steps are necessary to alert health care practitioners of the differences." FDA Decision, at 17. The FDA's failure to meaningfully consider requiring a risk management plan or to explain why it chose not to do so was arbitrary and capricious. *Gulf Power Co. v. FERC*, 983 F.2d 1095, 1099 (D.C. Cir. 1993) ("A showing that the agency has not considered relevant factors, examined alternative courses of action or made a rational policy choice can be sufficient" to establish that the agency action was arbitrary.).

* * * *

To Wyeth's knowledge, FDA's action here is without precedent. If upheld, it will open the door to more approvals of generic pharmaceutical products that cannot safely be administered in essentially the same way as the innovator drug. There may be more generics but also more harmful medication errors. The public fisc may benefit in the short term, but the public health will suffer. The central issue in this case is whether, despite the absence of any record evidence on which the Agency could have concluded that the approval of Orchid's generic adequately protects the public against serious medication errors, the Agency's decision to approve a generic with different ingredients, different labeling, and different compatibility with a common diluent in widespread use in emergency rooms was lawful. Wyeth submits the answer is clearly no. At a minimum, Wyeth "has raised serious legal questions going to the merits." *Population Inst. v. McPherson*, 797 F.2d 1062, 1078 (D.C. Cir. 1986) (citation omitted).

## II. WYETH WILL SUFFER IRREPARABLE HARM ABSENT PRELIMINARY INJUNCTIVE RELIEF.

Wyeth will be irreparably harmed if an injunction is not granted and FDA's decision is found to be erroneous. First, Wyeth is threatened with irreparable injury to its reputation and goodwill among healthcare providers and patients. A physician prescribes Zosyn with the expectation that it will provide safe and effective treatment to the patient. The patient likewise expects the product to perform safely and effectively. If Orchid's generic formulation is substituted for Zosyn and safety and efficacy issues arise due to the differences in formulation and drug labeling discussed *supra*, those problems could be associated with and attributed to the innovator product, Zosyn. In the first nine months of 2009, tens of thousands of patients likely received simultaneous administration of reformulated Zosyn with LRS. Friedrich Declaration, at ¶ 16; Wu Declaration, ¶¶ 7, 17; Ex. 20, 6/8/07 Levitt Letter to FDA, at 6. With usage levels like these, the probability of an erroneous substitution of a non-compatible generic product for the compatible reformulated Zosyn is extremely high. Such incidents would irreversibly and irreparably harm Wyeth's reputation and goodwill in the medical community. *See, e.g., Honeywell, Inc. v. Consumer Prod. Safety Comm'n*, 582 F. Supp. 1072, 1078 (D.D.C. 1984) (stating that injury to goodwill, reputation, and competitive position constitute irreparable harm); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1381 (Fed. Cir. 2006) (loss of good will constitutes irreparable harm); *Morgan Stanley DW Inc. v. Rothe*, 150 F. Supp. 2d 67, 77 (D.D.C. 2001) (damage to relationships with customers is irreparable harm). In addition, Wyeth may be exposed to product liability and negligence claims, further damaging its reputation and goodwill, based on any harm or injury caused by Orchid's generic drug product. Recently, a California court held that a pioneer drug company may be liable for certain injuries caused by generic versions of the pioneer drug. *See Conte*, 168 Cal. App. 4th 89. An injunction is necessary to

prevent the harm to patients, and to Wyeth's reputation, that would be caused by these circumstances.

Wyeth will also suffer irreparable economic harm if FDA's decision is found to be erroneous. Wyeth has invested enormous resources to bring Zosyn to market, and Zosyn has gained wide acceptance as a safe and effective intravenous antibiotic. As a direct result of FDA's unlawful action, Zosyn will quickly lose market share, substantial customer relationships, and revenue. *See generally* Declaration of Lewis L. Barrett. Once a generic drug is approved, it quickly saturates the market. *See, e.g.*, *CollaGenex Pharms., Inc. v. Thompson,* No. 03-1405 (RMC), 2003 U.S. Dist. LEXIS 12523, at *32 (D.D.C. July 22, 2003) ("It is not at all difficult to foresee that [the pioneer drug company's] market position would collapse as soon as one or more generic drugs became available."); *In re Cardizem CD Antitrust Litig.*, 200 F.R.D. 326, 340-41 (E.D. Mich. 2001) (describing predictable pattern of pioneer market share loss of up to 90% upon entry of competing generics). When this happens, an innovator drug may suffer irreversible price and market erosion. *Sanofi-Synthelabo*, 470 F.3d at 1382. These losses cannot be recovered from the government or any other party: an aggrieved party has no private damages action against the FDA for violation of the FDCA. *Berkowitz v. United States*, 486 U.S. 531, 535 (1988) (citing 28 U.S.C. § 2680(a)); *Serono Labs., Inc. v. Shalala*, 974 F. Supp. 29, 36 (D.D.C. 1997), *vac'd on other grounds*, 158 F.3d 1313 (D.C. Cir. 1998).

This Court has specifically recognized the devastating effect an erroneous approval of ANDAs can have on the innovator drug company:

> It is not at all difficult to foresee that [an innovator's] market position would collapse as soon as one or more generic drugs became available. [The innovator] would lose its head start in the market and its continued viability would be at issue. It could never recoup from FDA any losses that would occur . . . . These are the kinds of circumstances in which irreparable harm has been found.

*CollaGenex*, 2003 U.S. Dist. LEXIS 12523, at *33 (granting preliminary injunction to innovator manufacturer). This harm, while economic in nature, is irreparable. *Id.* at *33; *Express One Int'l, Inc. v. U.S. Postal Serv.*, 814 F. Supp. 87, 91 (D.D.C. 1992) (granting injunctive relief after finding that plaintiff would face non-recoverable monetary loss); *Woerner v. U.S. Small Bus. Admin.*, 739 F. Supp. 641, 650 (D.D.C. 1990) ("[Plaintiffs] claim, persuasively, irreparable injury because the government is immune from damage suits...."); *Hoffman-Laroche, Inc. v. Califano*, 453 F. Supp. 900, 903 (D.D.C. 1978) (granting injunctive relief because "plaintiff will suffer loss of sales and good will for which it would have no right of recourse, and thus its injury will be irreparable").

## III. NEITHER FDA NOR ANY GENERIC DRUG MAKER WILL SUFFER SUBSTANTIAL HARM IF AN INJUNCTION IS GRANTED.

It is also the case that neither FDA nor Orchid will suffer substantial harm if preliminary relief is granted. FDA has a statutory duty to ensure that the new innovator drugs it approves are safe and effective and that the generic drugs it approves can safely be administered in the same way. FDA also expects that its decisions will be subject to judicial review. *See, e.g.*, 5 U.S.C. § 706(2). The grant of an injunction pending judicial review of FDA's decision in this case poses no unusual burden or disadvantage for the Agency.

As for Orchid, it is not entitled to market a drug if FDA has violated the law in approving the drug, and so again, there is no risk of cognizable harm if Wyeth were to prevail in this action. To be sure, if Wyeth does not prevail, an injunction would delay the marketing of the generic Zosyn substitutes. But Orchid and the other generic drug manufacturers who have submitted citizen petitions have already had to wait several years for FDA's decision, and any additional delay occasioned by this proceeding would be relatively short. Additionally, Orchid had notice of the safety and efficacy issues raised by its proposed product through the filing of the various

citizen petitions and comments in this case. Any harm suffered by Orchid while this Court considers the merits of this case is temporary and minor compared with the irreparable harm that would be suffered by Wyeth and by patients who might receive Orchid's product in an IV line with LRS if an injunction were denied. *See, e.g.*, *CollaGenex*, 2003 U.S. Dist. LEXIS 12523, at *31-32 (holding that an ANDA applicant may suffer some harm from entry of an injunction, but that the generic company's large size, resources, and limited investment in its generic drug makes the harm comparatively minimal).

## IV. THE PUBLIC INTEREST WOULD BE FURTHERED BY GRANTING INJUNCTIVE RELIEF.

Finally, the public interest will be furthered by an injunction. FDA's core function is the promotion and protection of the public health. *See* 21 U.S.C. §393(b); *see also* FDA's "Mission Statement," *available at* <http://www.fda.gov/AboutFDA/whatwedo/Default.htm> ("The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, [etc.,]..."). There is a substantial public interest in ensuring that FDA follows the law in approving generic drugs and also that the Agency maintains consistent and dependable standards in which the public can have confidence. *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("[T]here is a strong public interest in meticulous compliance with the law by public officials."). That interest is heightened in the case of generic drug approvals given that generic drugs do not undergo the same degree of preclinical or clinical testing, and safety and efficacy are measured by equivalence to a branded reference drug. The public interest is not served by the unlawful approval of generic drugs that are not the same as the innovator drug and cannot safely be used in the same manner. *See* H.R. Rep. No. 98-857(1), at 21 ("[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.").

In addition, approval of a generic version of Zosyn that is not safely interchangeable with the branded reference drug poses serious public health risks. Most significantly, the clinical differences between Zosyn and the approved generic version of Zosyn creates a significant risk of confusion about whether the drug can safely be co-administered with LRS.

If FDA is wrong that these risks would be adequately mitigated by the use of the old Zosyn labeling for the generic substitute, and no injunction is granted, patients will suffer. On the other hand, if this Court ultimately affirms FDA's decision, but generic approval is stayed by the grant of an injunction pending that decision, the harm to the public would be minimal, consisting of a delay in the availability of a potentially cheaper but incomplete substitute for Wyeth's drug.[20] In any event, as Congress understood in imposing the sameness requirement for generic drugs, the public interest in cheaper drugs is outweighed by the significant public health risks posed by allowing a generic drug with different labeling and drug compatibility as its listed brand name counterpart into the marketplace. *See Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128, 131 (D.D.C 1997) (holding that the faithful application of the Hatch-Waxman Act outweighs the public interest in a marginal increase in the availability of low-cost generic drug products to American consumers).

The public health risks are real and non-speculative. Zosyn is one of the most widely used intravenously administered antibiotic drugs in the United States. It is used in patients who are gravely ill and in urgent need of efficacious, broad-spectrum resistance to bacterial infection. Based on third-party data, Wyeth estimates that, in 2006, Zosyn was concomitantly administered

[20] In this regard, it is worth noting that Orchid's product has been granted 180-day exclusivity as part of this approval, and its CEO has stated publicly that he does not plan to reduce the product's price during this period. Ex. 21 ("Orchid gets USFDA nod; stock up 25%," *available at* <www.moneycontrol.com>).

with LRS in about 104,832 patients. 6/8/07 Levitt Letter, at 6; Friedrich Declaration, at ¶ 16. Wyeth believes that nearly half (43%) of patients who received Zosyn with LRS received them simultaneously. *Id.*

In her comments to FDA, Dr. Joshi noted that it was "common practice to hang resuscitative fluids such as Lactated Ringer's solution with Zosyn in the same IV Port." Ex. 1, Joshi Letter, at 2. According to Dr. Joshi, not only would any generic formulation that cannot be co-administered with LRS represent a "step backward" in patient care, but there would also be significant risks associated with the concurrent marketing of that formulation with Zosyn:

> In my professional judgment, the decision by FDA to approve generic versions of piperacillin-tazobactam that have a different drug compatibility profile compared to the reformulated version of Zosyn marketed by Wyeth presents an undue and unnecessary risk to patients. Especially in critical care settings, the risk that doctors will confuse generic versions of piperacillin-tazobactam with Wyeth's reformulated version is high, and this can result in less effective antibiotic treatment where it is critically necessary.

Joshi Declaration, at ¶ 24.

Dr. Coleman Rotstein of McMaster University in Ontario, Canada, also stated that co-administration of Zosyn with LRS was common, and advantageous to treat certain conditions. Ex. 2, Rotstein Letter, at 1. According to Dr. Rotstein, "any chance of incompatibility or inactivation when the drugs are combined together ... must be prevented at all costs." *Id.*

Given the widespread use of Zosyn, and its frequent combination with LRS in critically ill and vulnerable patients, there is a strong public interest in ensuring that FDA has followed the law, that FDA's action is not arbitrary and capricious, and that any generic version of Zosyn can be safely substituted for Wyeth's formulation.

## CONCLUSION

For the foregoing reasons, Wyeth respectfully requests that this Court issue a preliminary injunction or, in the alternative, a temporary restraining order requiring FDA to withdraw or suspend its approval of Orchid's ANDA, and to suspend the approval of any other ANDAs for generic products that are based on the superseded formulation of Zosyn, which are not shown to be compatible with LRS, and which include labeling changes that reflect that incompatibility.

Respectfully submitted,

September 22, 2009

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*