Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101

Geoffrey M. Levitt
VP & Chief Counsel, Regulatory
and Research
Legal Division
484-865-8598
levittg@wyeth.com

Wyeth

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Wyeth Pharmaceuticals ("Wyeth") submits this citizen petition under section 505 of the Federal Food, Drug, and Cosmetic Act (the "Act") and 21 C.F.R. § 10.30 to request that Food and Drug Administration ("FDA") approval of any abbreviated new drug application ("ANDA") or 505(b)(2) application relying on Zosyn® (piperacillin and tazobactam for injection) as its reference product be contingent upon the proposed product (a "Generic Product") (1) complying with U.S. Pharmacopeia standards on particulate matter in injectable drugs when tested under expected conditions of actual use; and (2) exhibiting the same compatibility profile as Zosyn®. If a Generic Product demonstrates a compatibility profile that is different than that of Zosyn® and if, despite this difference, FDA approves such a product, FDA should require the manufacturer of the product to implement an effective risk minimization action plan to keep healthcare practitioners aware of those differences.

I. ACTION REQUESTED

Wyeth requests that FDA refrain from approving any application for a Generic Product unless:

(1) the Generic Product complies with the U.S. Pharmacopeia standards on particulate matter in injectable drugs ("Particulate Matter in Injections") in General Chapter <788> under the variety of conditions of metal ion and pH levels found in the commercial diluents permitted for use in its label; and

(2) the Generic Product exhibits the same compatibility profile as Zosyn®, particularly with respect to compatibility with Lactated Ringer's Solution and the aminoglycoside antibiotics amikacin and gentamicin.

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If the Generic Product does not exhibit the same compatibility profile as Zosyn® and FDA chooses to approve the product despite this difference, Wyeth requests that such approval be conditioned upon the applicant's implementation of a risk minimization action plan to address the confusion that would necessarily arise as a result of such difference.

II. BACKGROUND

A. Zosyn® Products

Zosyn® is a combination antibacterial product used for treating certain infections. Wyeth distributes the product in several presentations: (1) standard vials, (2) ADD-Vantage® vials, (3) pharmacy bulk vials, and (4) Galaxy® containers. When distributed in vials, Zosyn® is in the form of a lyophilized powder; when in Galaxy® containers, it is in the form of a frozen solution.

To use a powdered version of Zosyn®, the product is first reconstituted in the vial using a compatible diluent, as identified in the package insert.[1] The reconstituted Zosyn® solution is then further diluted in a compatible intravenous solution, as identified in the package insert, by transferring the product to an infusion bag.[2] After reconstitution in the vial and dilution in the infusion bag, Zosyn® is administered to patients by intravenous infusion.

Wyeth recently reformulated Zosyn® in order to meet U.S. Pharmacopeia particulate standards across all admixture conditions commonly encountered in the clinical setting. The reformulated version contains edetate disodium dihydrate ("EDTA") and citric acid monohydrate, two ingredients not included in the original formulation. These changes resulted in an expanded compatibility profile for Zosyn®, including compatibility with Lactated Ringer's Solution and two commonly used aminoglycoside antibiotics, amikacin and gentamicin. Lactated Ringer's Solution is commonly used as an intravenous diluent and may also be used for fluid resuscitation after blood loss in trauma patients, in which case the reformulated version of Zosyn® may be co-administered. The ability to co-administer the reformulated product with amikacin and gentamicin is also

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[1] Compatible diluents are listed in the Zosyn® label as: (i) 0.9% sodium chloride for injection, (ii) sterile water for injection, (iii) dextrose 5%, (iv) bacteriostatic saline/parabens, (v) bacteriostatic water/parabens, (vi) bacteriostatic saline/benzyl alcohol, and (vii) bacteriostatic water/benzyl alcohol.

[2] Compatible intravenous solutions listed in the Zosyn® label include: (i) 0.9% sodium chloride for injection, (ii) sterile water for injection, (iii) dextrose 5%, (iv) dextran 6% in saline, and (v) Lactated Ringer's Solution (compatible only with reformulated Zosyn® containing EDTA).

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noteworthy in the context of diseases such as nosocomial pneumonia, for which the concomitant use of the product and an aminoglycoside antibiotic is indicated.

Prior to the reformulation, Zosyn® was not compatible with either aminoglycoside antibiotics or Lactated Ringer's Solution. In fact, the approved product labeling for the original version of Zosyn® informed users in a bolded, all capitals statement that the product was not compatible with Lactated Ringer's Solution. The original labeling also instructed users to exercise care to administer aminoglycosides separately from the drug product because *in vitro* mixing of the original version of Zosyn® with aminoglycosides could result in inactivation of the aminoglycoside. The approved product labeling for the reformulated version of Zosyn® was revised to reflect the product's new compatibility with Lactated Ringer's Solution, amikacin, and gentamicin. The labeling now informs users that reformulated Zosyn® is compatible with Lactated Ringer's Solution and may also be co-administered with gentamicin and amikacin via a Y-site or multiple-port infusion system.

B. Particulate Matter in Injectable Products

Particulate matter in parenteral products can arise either exogenously or endogenously. Exogenous particulates are those that result from sources other than the drug product itself. Examples of sources of exogenous particulates include insoluble compounds in intravenous bags and bits of septa and corings that can be introduced when piercing drug containers with hypodermic needles.

Endogenous particulates, on the other hand, arise from the product itself. In injectable products, endogenous particulates are generally the result of chemical reactions that occur during processing, storage, or preparation of the product for patient use. Minimization of endogenous particulates requires extensive testing and analysis of the product under all conditions of potential use and adjusting the product formulation or manufacturing process accordingly.

Although limitations on particulate matter have been in place for many years, injectable products inevitably contain very small amounts of particulate matter. Infusion of particulates that are too large or too numerous, however, can cause adverse health effects.[3] Manufacturing specifications therefore limit the amount and size of acceptable particulate matter. United States specifications are set forth in USP <788>.

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[3] *See* Nrapendra Nath et al., *Particulate Contaminants of Intravenous Medication and the Limits set by USP General Chapter <788>*, 30 Pharmacopeial Forum 2272 (2004). Attached as Exhibit A.

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Prior to 1995, the USP <788> particulate limits were no more than 10,000 particles ≥10μm and no more than 1,000 particles ≥25μm.[4] In 1995, USP updated <788> to tighten the limits to no more than 6,000 particles ≥10μm and no more than 600 particles ≥25μm. The reduction in the limits was due in large part to the increasing body of clinical evidence indicating that intravenous treatments with lower levels of particulate contamination are associated with a reduction in the incidence of adverse events.[5] Similar particulate limits have been instituted in both Europe and Japan.[6]

III. STATEMENT OF GROUNDS – GENERIC PRODUCTS SHOULD BE REQUIRED TO COMPLY WITH USP <788>

A. Causes of Endogenous Particulate Formation in Zosyn®

Endogenous particulate formation in Zosyn® can generally occur in three ways. First, soluble piperacillin sodium can convert into an insoluble free acid (piperacillin monohydrate) when Zosyn® is prepared using an acidic diluent (see Figure 1). In addition, because solutions made from piperacillin and tazobactam that are close to expiration can have low pH due to acidic byproducts that occur naturally over time, a somewhat acidic diluent used with such a product may result in particulate formation even if the same diluent would not cause that outcome with fresher product.

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[4] These were the USP <788> particulate limits in effect when the original formulation of Zosyn® was approved.

[5] KH Falchuck, et al., *Microparticulate-induced phlebitis. Its prevention by in-line filtration*, 312 New Eng. J. Med. 78 (1985); Hans-anton Lehr, et al., *Particulate Matter Contamination of Intravenous Antibiotics Aggravates Loss of Functional Capillary Density in Postischemic Striated Muscle*, 165 Am. J. Respiratory and Critical Care Med. 514 (2002); R. Leon Longe, *Particulate Contamination in Selected Parenteral Drugs*, 27 Can. Anesthesia Soc'y J. 62 (1980). Attached as Exhibits B, C, and D, respectively.

[6] European Pharmacopoeia, General Notices § 2.9.19 "*Particulate contamination: sub-visible particles*"; Japanese Pharmacopoeia, General Rules for Preparations § 11 (13) "*Injections.*"

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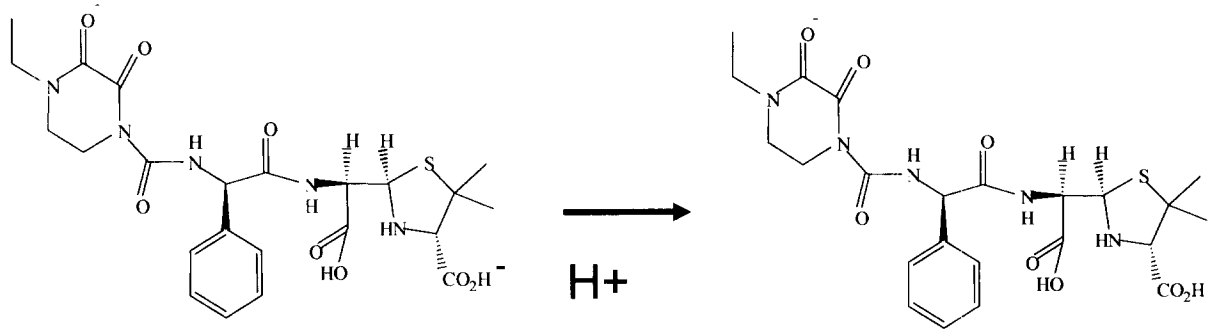
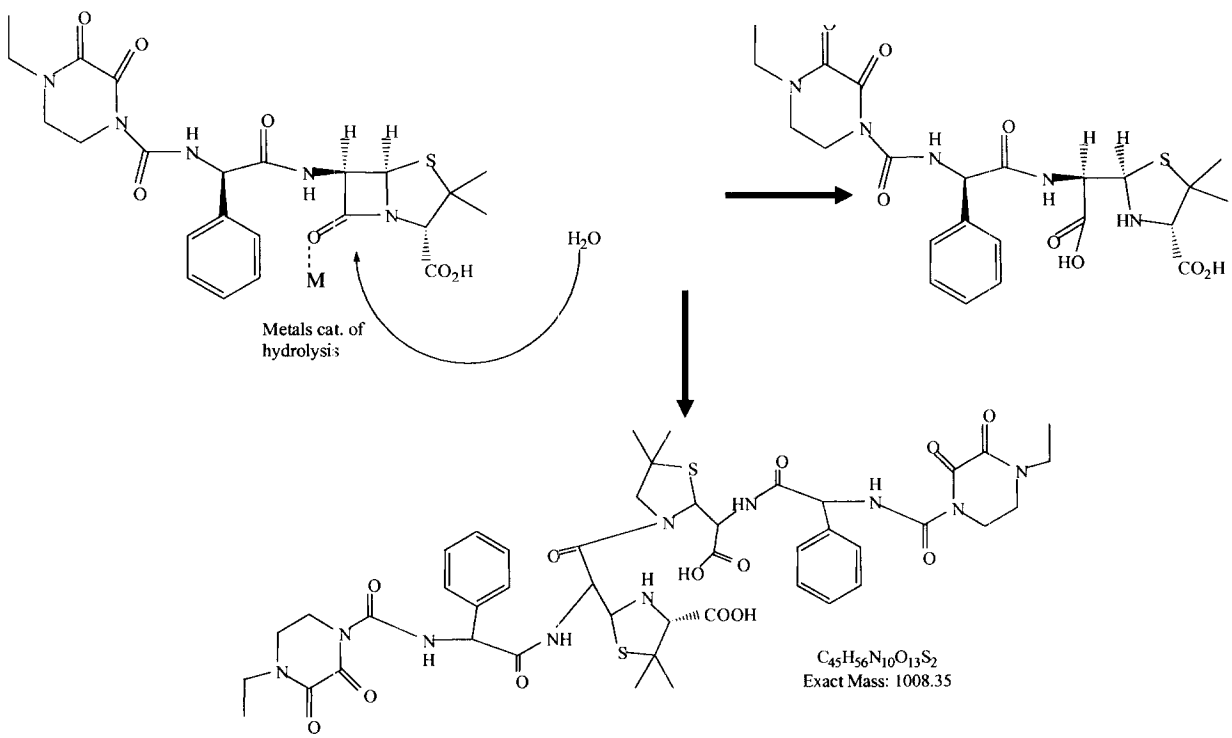
Figure 1
Conversion of Soluble Piperacillin Sodium into an Insoluble Free Acid



Second, the combination of Zosyn® of any age with acidic diluents can cause shifts in pH. These shifts can affect particulate formation by means of hydrolysis, which occurs when acidic attack on the piperacillin carbonyl group opens the compound's beta-lactam ring. This, in turn, creates a chemically reactive site with an affinity for amine groups. Because piperacillin contains amine groups, dimers of piperacillin, which are insoluble, can form and increase levels of particulate matter (see Figure 2).

Figure 2
Hydrolysis of Piperacillin Followed by Formation of Piperacillin Dimer



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Third, metals such as zinc and iron accelerate the hydrolysis of piperacillin and increase the rate of particulate formation. This chemical catalysis occurs because the presence of metal ions extends the time after hydrolysis during which the piperacillin molecule remains in a chemically reactive state. This directly results in a lengthening of the period of time in which insoluble dimers of piperacillin can form. In addition, because metal ions are merely catalysts for the reaction and are not consumed as a part of the hydrolysis of piperacillin, they remain available to catalyze additional reactions, which further increase the amount of particulate formation.[7]

Metal ion residue can originate from a variety of sources, including chemical syntheses, addition of excipients, contact with polymeric or elastomeric containers (including diluent bags), and contact with processing vessels and related piping. The most significant variable appears to be intravenous solutions used to administer drugs, as those solutions tend to have widely varying levels of metal ions.

B. Variability in Metal Ion Concentration and pH Level in Commercially Available Diluents Can Affect Particulate Matter Formation in Zosyn®

Wyeth tested over fifty lots of commercial diluents and found that typical zinc levels for those diluents range from 0.0 ppm to 0.8 ppm (see Figure 3).

[7] Metal catalyzed degradation of piperacillin has been documented in scientific literature. *See* Kaori Bandoh, et al., *Metal Induced Degradations of β-Lactams*, 39 Chemotherapy 315 (1991). Attached as Exhibit E.

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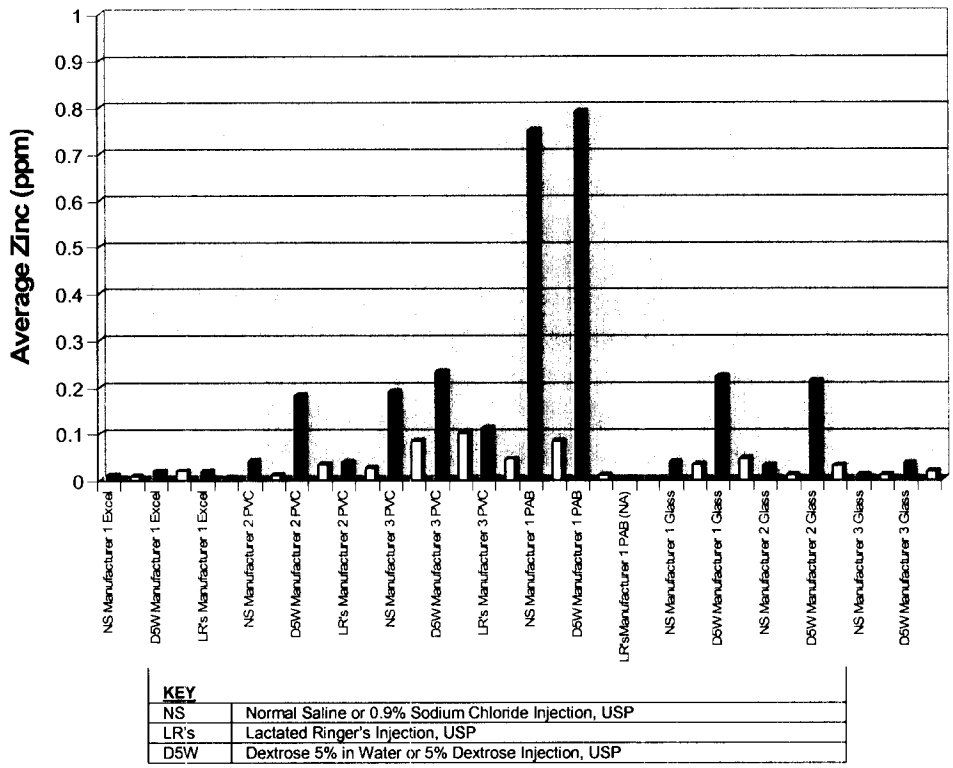
Figure 3
Highest (Black) and Lowest (White) Zinc Levels
Detected In Commercial Diluents, by Manufacturer and Container Type



KEY	
NS	Normal Saline or 0.9% Sodium Chloride Injection, USP
LR's	Lactated Ringer's Injection, USP
D5W	Dextrose 5% in Water or 5% Dextrose Injection, USP

Metal ion concentration varied not only across manufacturers, but also within lots of the same product produced by the same manufacturer. For example, testing of thirteen lots of 5% dextrose for injection, USP, all manufactured by the same company, yielded an average zinc concentration of 0.4 ppm, with levels as low as 0.0 ppm and as high as 0.8 ppm.

In addition, Wyeth found that zinc ions were present not only in the diluents themselves, but also in the diluent bags. The zinc levels in diluent bags are additive to the concentrations found in the diluent.

Similarly, pH levels in commercial intravenous fluids also vary substantially, even from lot to lot from the same manufacturer. For example, the product information for products manufactured by B. Braun indicates the following, generally acidic ranges of pH levels:

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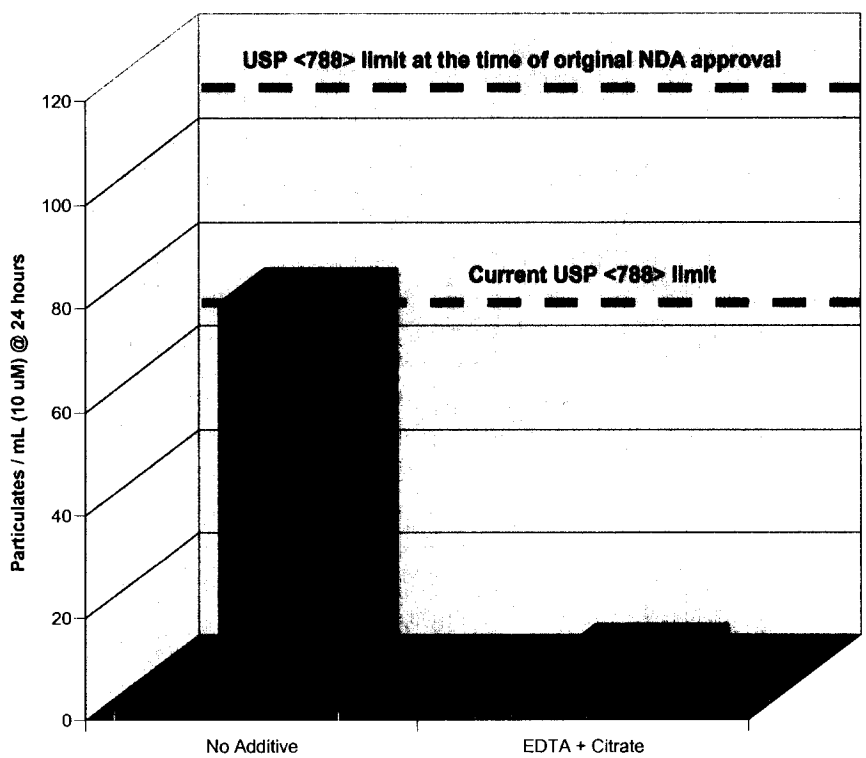
- 5% dextrose, USP – pH from 3.5 to 6.5
- sterile water for injection, USP – pH from 5.0 to 7.0
- sterile 0.9% sodium chloride for injection, USP – pH from 4.5 to 7.0
- dextran 6% in saline, USP – pH from 4.0 to 7.0.

In general, Wyeth learned that the highest levels of particulate matter occur when the diluent has a low pH level and/or a high level of metal ions. During the process of reformulating Zosyn®, Wyeth tested the reformulated product with diluents exhibiting those characteristics in order to ensure that the product would comply with USP <788> under all foreseeable use conditions. Because of its extensive testing and analysis, Wyeth was able to create a reformulated version of Zosyn® that complies with USP <788> under all extremes of pH and metal ion concentration that exist in clinical practice. By adding EDTA as a chelating agent and citric acid monohydrate as a pH buffer to the original formulation, Wyeth significantly reduced particulate formation in Zosyn® (see Figure 4).

Figure 4
Effect of Chelating Agent/Buffer Complex
on Formation of Particulates ≥10μm in Zosyn® at 24 Hours



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C. Any Generic Product Referencing Zosyn® Should Be Rigorously Tested Under Expected Conditions of Use to Ensure Compliance with USP <788>

Due to the wide variability in the pH and metal ion concentration of commercial diluents, Wyeth's original Zosyn® product was susceptible to particulate formation under certain circumstances. In addition, the original product was vulnerable to excess particulate formation toward the end of its shelf life as it became more acidic. Wyeth's appreciation of FDA's concerns regarding particulate matter levels prompted it to reformulate Zosyn® such that the product would be robust enough to satisfy the tightened USP particulate specifications under all expected conditions of use. The reformulated version of the drug was thus subjected to rigorous testing and analysis to ensure that it would meet the specifications set forth in USP <788>, regardless of the metal ion concentration or pH of the diluent used and regardless of whether the product was used near its expiration date.

Given the broad spectrum of manufacturing practices employed by various manufacturers, sponsors of Generic Products should be required to conduct wide-ranging testing and analysis similar to that conducted by Wyeth in order to ensure the safety, quality, and purity of their products. Section 505(j)(4) of the Act provides, with respect to ANDAs, that the product involved cannot be approved if:

> the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.[8]

Thorough and extensive testing under multiple conditions of expected use should be required in order to demonstrate a Generic Product's full compliance with the particulate limitations in USP <788>. Demonstrating compliance by using a carefully selected lot of diluent with optimal characteristics (e.g., neutral pH and low metal concentration), or even by using a randomly selected lot of diluent, should not be permitted because appropriate testing conditions require testing the product under the least desirable, though expected, diluent conditions. If a Generic Product is not tested for particulate matter formation under a range of circumstances (e.g., dilution with acidic diluents with high metal ion

[8] A similar provision appears in section 505(d)(3) with respect to applications submitted under section 505(b).

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concentration), it will be unclear whether the product will meet USP specifications when used in clinical practice.

In order to avoid instances of potentially harmful excess particulate matter formation, as a condition of approval, FDA should require Generic Products to meet USP <788> particulate limits when tested with all diluents permitted in the product's labeling and when using samples of each diluent from different manufacturers. In this way, Generic Products will be tested against the major factors influencing particulate formation, namely, pH levels and metal ion concentrations. Results of this testing should also substantiate all storage times and temperatures listed in a Generic Product's labeling. A proposed test protocol for Generic Products is attached as Appendix A.

FDA should approve a Generic Product only if it is robust enough to satisfy the particulate test in USP <788> under all possible use conditions permitted in its label and all extremes of pH and metal ion concentration that exist in practice. Given the well-established safety issues arising as a result of excess particulate matter in injectable products, to do otherwise would be at odds with the best interests of the patient population.

IV. STATEMENT OF GROUNDS – GENERIC PRODUCTS SHOULD BE REQUIRED TO EXHIBIT THE SAME COMPATIBILITY PROFILE AS ZOSYN®

FDA should refrain from approving applications for Generic Products unless such products exhibit the same compatibility profile as Zosyn®, particularly with respect to Lactated Ringer's Solution and the aminoglycoside antibiotics amikacin and gentamicin.

A. Generic Products that Satisfy USP <788> May Not Demonstrate the Same Compatibility Profile as Zosyn®

A Generic Product that is robust enough to satisfy the USP <788> particulate test under all expected conditions of use may exhibit a different compatibility profile than Zosyn® with respect to Lactated Ringer's Solution, amikacin and gentamicin. This is possible because the conversion of piperacillin sodium into piperacillin monohydrate (described in Figure 1) and the hydrolysis of piperacillin (described in Figure 2) not only cause particulate formation, but also affect a piperacillin product's compatibility profile. Focusing on these chemical processes to reduce particulate formation in a Generic Product may not, however, yield a product that has the same compatibility profile as Zosyn®. Therefore, although the inclusion of EDTA as a chelator and citric acid monohydrate as a buffer in

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Zosyn® both addresses the particulate formation issue and expands its compatibility profile, a Generic Product that does not include EDTA and citric acid monohydrate could comply with USP <788> but not exhibit the same compatibility profile as Zosyn®, or vice versa.

B. Generic Products that Exhibit Different Compatibility Profiles from Zosyn® Would Create Public Health Risks

As discussed earlier in this citizen petition, Zosyn® was recently reformulated. The reformulated product demonstrates an expanded compatibility profile in that (1) it may be combined *in vitro* with the aminoglycoside antibiotics amikacin and gentamicin and (2) it is compatible with Lactated Ringer's Solution. Approval of a Generic Product that is not compatible with these products would create public health risks because such Generic Products are generally required to have the same conditions of use as their brand-name counterparts.[9] As such, healthcare professionals would expect to use Generic Products interchangeably with Zosyn®. Consequently, a Generic Product that does not have available the same conditions of use as Zosyn® is likely to cause confusion among practitioners. Furthermore, healthcare practitioners who administer drugs are often not the same individuals who decide whether a healthcare facility will use a brand-name drug or a generic substitute. The separation of decision-makers from practitioners also has the potential to cause confusion among practitioners as to whether they are using Zosyn® or a Generic Product.

In the case of a Generic Product that exhibits different compatibility characteristics as Zosyn®, a practitioner's confusion as to whether Zosyn® or the Generic Product is being used may result in substandard patient care. Consider, for example, a physician who uses Zosyn® with Lactated Ringer's Solution. It is foreseeable that this physician, or a pharmacist or nurse, might (1) substitute the Generic Product for Zosyn® and (2) assume, as is natural to do, that the Generic Product can be used in the same manner as Zosyn®. The practitioner would then continue to use Lactated Ringer's Solution for reconstitution, resulting in the inactivation of the active ingredient of the Generic Product and suboptimal patient care, at best.

Similarly, if the practitioner in the example above generally used Zosyn® with amikacin or gentamicin, improper substitution of the Generic Product for Zosyn could lead to inactivation of the aminoglcycoside and potential under-dosing of

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[9] 21 C.F.R. § 314.92(a)(1).

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the patient.[10] This is especially problematic in the context of diseases such as nosocomial pneumonia, for which the concomitant use of Zosyn® and an aminoglycoside is indicated.

These examples illustrate the fact that approval of Generic Products with compatibility profiles differing from that of Zosyn® is likely to cause confusion among healthcare practitioners, which will lead to an increased risk of improper substitution of such Generic Products for Zosyn®. This, in turn, will increase the risk of reduction in the efficacy of drug products. The continuing nature of these risks and their effect on patient safety should compel the rejection of applications for Generic Products that are not compatible with Lactated Ringer's Solution, amikacin and gentamicin.

C. FDA Regulations Require Generic Products To Duplicate the Current Zosyn® Formulation

Under FDA regulations, a generic injectable drug must generally contain the same inactive ingredients as the reference drug.[11] Differences in preservatives, buffers, and antioxidants are permitted, but the applicant must demonstrate that such differences do not affect the safety or efficacy of the proposed drug.[12] Other differences in chemical composition are not permitted.[13]

Citric acid monohydrate was incorporated in the reformulated Zosyn® product to control the pH of the reconstituted drug. Because citric acid monohydrate acts as a buffer, a generic product based on Zosyn® could, under the regulations, omit citric acid monohydrate or use a different buffer, provided that the resulting product was equally safe and effective and met all other requirements, including limitations on particulate matter. If, however, a change in the buffer results in a different compatibility profile, the Generic Product would not be as safe and

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[10] The *in vivo* and *in vitro* inactivation of certain aminoglycosides by beta-lactam antibiotics such as Zosyn® is well documented. *See* Richard H. Glew & Rosemary A. Pavuk, *Stability of Gentamicin, Tobramycin, and Amikacin in Combination with Four β-Lactam Antibiotics*, 24 Antimicrobial Agents and Chemotherapy 474, 474 (1983); DeVon C. Hale et al., *In-vitro Inactivation of Aminoglycoside Antibiotics by Piperacillin and Carbenicillin*, 74 Am. J. Clinical Pathology 316 (1980); C.E. Halstetson et al., *Effect of Concomitant Administration of Piperacillin on the Dispositions of Isepamicin and Gentamicin in Patients with End-Stage Renal Disease*, 36 Antimicrobial Agents and Chemotherapy 1832 (1992); Juan N. Walterspiel et al., *Comparative Inactivation of Isepamicin, Amikacin, and Gentamicin by Nine β-Lactamase Inhibitors, Cilastatin and Heparin*, 35 Antimicrobial Agents and Chemotherapy 1875, 1877 (1991). Attached as Exhibits F, G, H and I, respectively.

[11] 21 C.F.R. § 314.94(a)(9)(3).

[12] *Id.*

[13] *See* 21 C.F.R. § 314.127(a)(8)(ii)(B).

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effective as Zosyn® and therefore could not be approved. EDTA functions as a chelating agent in Zosyn®, and not as a preservative, buffer, or antioxidant, and therefore, under the regulations, must be used in any Generic Product.

Any waiver of the regulations would be inappropriate. To protect patient safety, it is essential that the compatibility profile of any Generic Product be the same as that of Zosyn®.

V. STATEMENT OF GROUNDS – APPROVAL OF A GENERIC PRODUCT THAT EXHIBITS A DIFFERENT COMPATIBILITY PROFILE THAN ZOSYN® SHOULD BE CONTINGENT UPON THE SPONSOR'S IMPLEMENTATION OF A RISKMAP

The risks described in Section IV cannot be adequately addressed by routine risk management measures. Even if only one product (either Zosyn® or the Generic Product) will be available for use at any given healthcare facility, many healthcare providers have clinical privileges at multiple healthcare facilities. This highlights the need to manage the public health risk inherent in allowing a Generic Product with a different compatibility profile on the market when healthcare providers could incorrectly assume its equivalence with Zosyn®. If, despite this risk, FDA approves applications for such Generic Products, FDA should require the applicants to take aggressive steps to minimize the health risks that their products will create by implementing a risk minimization action plan (a "RiskMAP"). Although continuous education and communication under a RiskMAP could reduce the risks associated with such Generic Products, Wyeth notes that such risks could not be completely eliminated.[14]

A. RiskMAPs Generally

In March 2005, FDA released three final guidance documents, each focusing on a different aspect of risk management: assessment of pre-marketing risk, assessment of post-marketing risk, and risk minimization.[15] The guidance documents define RiskMAPs as strategic programs "designed to meet specific

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[14] While a RiskMAP would reduce the risks, the labeling differences between Zosyn® and a generic product necessary to reflect compatibility differences would appear to raise safety issues that cannot be satisfactorily resolved through a RiskMAP alone. *Cf.* 21 C.F.R. § 314.127(a)(7) (protected matter cannot be omitted from the generic's product labeling if the omission would render the product less safe).

[15] *See* FDA, *Guidance for Industry: Premarketing Risk Assessment* (Mar. 2005); FDA, *Guidance for Industry: Good Pharmacovigiliance Practices and Pharmacoepidemiologic Assessment* (Mar. 2005); FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans* (Mar. 2005).

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goals and objectives in minimizing known risks of a product while preserving its benefits."[16] In these documents, FDA discusses several types of RiskMAP tools, including (1) education and outreach tools and (2) reminder systems.

FDA recommends education and outreach tools when routine risk minimization is known or is likely to be insufficient in minimizing product risks. These tools employ specific and targeted efforts "to increase appropriate knowledge and behaviors of key people or groups (e.g., healthcare practitioners and consumers) that have the capacity to prevent or mitigate the product risks of concern."[17] In addition, these tools can be used to explain how drug products should be used in order to maximize benefits (e.g., educating physicians about the effects of changes in temperature on the potency of a drug) and minimize risks (e.g., educating consumers to take drug products according to labeled instructions). Examples of tools in this category include informational letters to healthcare practitioners and professional or public notifications.

FDA recommends tools in the reminder-system category when targeted education and outreach tools are insufficient to minimize identified risks. These types of tools can "prompt, remind, double-check, or otherwise guide healthcare practitioners in prescribing, dispensing, receiving, or using a product in ways that minimize risk."[18] Tools in this category include training programs that test a healthcare provider's knowledge and understanding, specialized packaging to enhance safe use of the product, and specialized records such as prescription stickers that are used to attest that safety measures have been satisfied.

B. Wyeth's Risk Minimization Program

When Wyeth introduced the current formulation of Zosyn® to the market and discontinued the previous formulation, it anticipated that the switch could give rise to confusion among practitioners during the transition period. This was because the previous formulation, unlike the current formulation, was not compatible with Lactated Ringer's Solution and could not be combined *in vitro* with amikacin or gentamicin. Accordingly, Wyeth developed a comprehensive and detailed communication program to help practitioners differentiate between the two formulations during the estimated ten-week period in which both formulations were expected to be concurrently available in the market. Designed to minimize medical error and protect patient safety, the program was

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[16] FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, at 5.
[17] *Id.* at 8.
[18] *Id.* at 9.

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implemented in conjunction with the introduction of the current, reformulated version of Zosyn®.

The communication program consisted of many components and employed a multi-faceted approach. First, new materials were developed for Zosyn® sales representatives to help them understand the differences between the previous formulation and the current formulation and communicate those differences to practitioners. The materials included internal training resources, a flip-chart style visual aid, a compatibility flashcard, and an informational dosing card. These materials discussed in detail the compatibility information for the reformulated product with amikacin and gentamicin (Zosyn® dose amount and form, diluent volume, aminoglycoside concentration range, and acceptable diluents). They also noted the new compatibility with Lactated Ringer's Solution and pointed out the differences in packaging and National Drug Codes for the previous formulation and the current formulation. Over four hundred sales representatives were trained and certified on these materials, as well as on the new label for the product.

Second, the packaging for Zosyn® was redesigned to include a yellow background so that healthcare providers could easily distinguish between the packaging for the previous formulation and the reformulated version.

Finally, concurrently with the introduction of the reformulated product, Wyeth distributed a detailed letter announcing both the availability of the product and the expanded compatibility of the product. The letter was distributed through conventional direct-mail channels and via email to over 5,000 hospitals and more than 10,000 other recipients, including all Wyeth wholesalers and more than ninety percent of group purchasing organizations, long-term care facilities, managed care organizations, pharmacy benefit managers, and chain pharmacies. The letter, like the materials described above, both highlighted the expanded compatibility of the reformulated product and reminded practitioners that the original formulation does not have this expanded compatibility.

Wyeth thus employed a three-pronged approach in delivering its message about the important differences between the previous formulation of Zosyn® and the reformulated version: (1) using a direct-mail and email campaign notifying practitioners of the message; (2) providing an experienced sales force with the necessary tools to help deliver and reinforce the message; and (3) revising packaging so as to remind practitioners of the message at the time of use. This three-pronged approach helped ensure that healthcare providers remained aware of the differences between the two products, regardless of whether the different facilities to which they had clinical access used only one product or both products.

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C. Proposed RiskMAP For a Generic Product Based on Zosyn®

It was unnecessary for Wyeth's communication program to address the long term effects of having the previous formulation of Zosyn® and the reformulated version on the market because the two products were only expected to be concurrently available for a short period of time. The existence of a Generic Product that does not exhibit the same compatibility profile of Zosyn®, however, would create additional and sustained confusion in the marketplace among practitioners, particularly if use of Zosyn® with certain aminoglycoside antibiotics and Lactated Ringer's Solution is established as a standard practice during the extended period of time in which only Zosyn® is available. Therefore, a RiskMAP implemented by the sponsor of such a Generic Product should incorporate the steps taken by Wyeth as well as additional steps to ensure that the risk of confusion and improper administration of the Generic Product is minimized for as long as both products are in the marketplace.

A RiskMAP comprised of education, outreach, and reminder tools would minimize the risks associated with having Zosyn® and a Generic Product with a different compatibility profile on the market at the same time "without encumbering drug availability or otherwise interfering with the delivery of product benefits."[19] As such, it is essential that the sponsor of a Generic Product with a different compatibility profile establish a RiskMAP addressing the risks arising from such difference. Because manufacturers of generics typically do not interact with individual practitioners, it is all the more important that FDA require such a RiskMAP to include components directly communicating to this population. The RiskMAP should, throughout the life of the Generic Product, also include:

- distribution of information to healthcare practitioners, healthcare facilities, and those responsible for the bulk purchase of drug products communicating the differences between the Generic Product and Zosyn®;

- ongoing training programs for healthcare practitioners to raise awareness of the differences between the Generic Product and Zosyn®, with components designed to test the participant's knowledge and understanding of the topics covered;

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[19] *Id.* at 5.

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- press releases and periodic notifications in professional medical journals describing the differences between the Generic Product and Zosyn®;

- specialized product packaging to encourage correct use of the Generic Product and discourage incorrect use; and

- programs specifically addressing the risk of improper administration that is presented when a physician, pharmacist or nurse practices in two or more healthcare facilities, where one facility uses Zosyn® and the other uses the Generic Product.

D. RiskMAP Evaluation

A RiskMAP implemented by the sponsor of a Generic Product that differs from Zosyn® in its compatibility profile should be monitored and evaluated in order to identify areas for improvement. This kind of evaluation will help "ensure that the energy and resources expended on risk minimization are actually achieving the desired goals of continued benefits with minimized risks," which FDA has stated is the objective of RiskMAPs.[20] A RiskMAP containing an evaluation component would be consistent with the FDA recommendation that "every RiskMAP contain a plan for periodically evaluating its effectiveness after implementation."[21]

V. ENVIRONMENTAL IMPACT

Under 21 C.F.R. §§ 25.30(h) and 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

VI. ECONOMIC IMPACT

Information regarding the economic impact of this proposal will be submitted upon request by FDA following review of this petition.

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[20] *Id.* at 13.
[21] *Id.*

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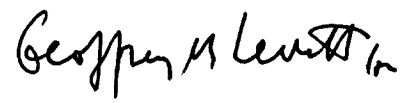
VII. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Geoffrey M. Levitt
Vice President & Chief Counsel
Regulatory and Research

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APPENDIX A

PROPOSED TEST PROTOCOL

1. OBJECTIVE AND SCOPE

The purpose of the study is to evaluate the chemical and physical compatibility of a piperacillin and tazobactam product with 4 intravenous diluents: 0.9% Sodium Chloride Injection, USP ("Sodium Chloride"), 5% Dextrose in Water, USP ("D5W"), Sterile Water for Injection, USP ("Sterile Water"), and Lactated Ringer's Injection, USP ("LRS").

The goal of this study is to determine if such admixtures meet United States Pharmacopoeia standards for particulate matter in injectable drugs as set forth in USP General Chapter <788> after storage times set forth in the label of the piperacillin and tazobactam product (e.g., 24 hours at room temperature and 7 days of refrigerated storage).

Testing will involve preparation of the highest and lowest concentrations of the piperacillin and tazobactam product available with each of the diluents listed above. The diluent bags used for the preparation of these samples will be tested prior to admixture for zinc content and pH. Samples will be prepared in bags with high zinc content (0.8 ppm or more). After the piperacillin and tazobactam product is admixed into the diluent, samples will be stored for either 24 hours at room temperature or for 7 days at 2 – 8 °C. Samples will be tested after storage.

Samples that yield fewer than 6,000 particles ≥10 μm in size and fewer than 600 particles ≥25 μm in size for both test periods will comply with USP <788> "Particulate Matter in Injections" as determined by light obscuration methodology.

2. MATERIALS

Table 1 sets forth examples of the materials to be used for this study (piperacillin and tazobactam product concentrations, diluents, and solution concentrations).

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Table 1

Concentration of Drug Product	Diluent	Solution Concentration
4.5 g	Sterile Water	80 mg/mL piperacillin plus 10 mg/mL tazobactam
4.5 g	Sodium Chloride	80 mg/mL piperacillin plus 10 mg/mL tazobactam
4.5 g	D5W	80 mg/mL piperacillin plus 10 mg/mL tazobactam
4.5 g	LRS	16 mg/mL piperacillin plus 2 mg/mL tazobactam
2.25 g	Sterile Water	40 mg/mL piperacillin plus 5 mg/mL tazobactam
2.25 g	Sterile Water	13.33 mg/mL piperacillin plus 1.67 mg/mL tazobactam
2.25 g	Sodium Chloride	13.33 mg/mL piperacillin plus 1.67 mg/mL tazobactam
2.25 g	D5W	13.33 mg/mL piperacillin plus 1.67 mg/mL tazobactam
2.25 g	LRS	8 mg/mL piperacillin plus 1 mg/mL tazobactam

3. METHODS

1. Method L-28156-55 (TR-V-05-020) HPLC Assay for Piperacillin and Tazobactam

2. Method (L17899-002)-Visual Appearance and Description of admixtures.

3. USP <788> Light obscuration Method (HIAC) for particle count of admixture samples

4. USP method for pH

5. A suitable test to quantify zinc and other transition metals in the 0.0 ppm to 5.0 ppm range with a precision of ±0.01ppm

4. PROCEDURE

Perform steps 1 – 5 below using Sodium Chloride, D5W, Sterile Water and LRS.

1. Test the pH and zinc content of each diluent bag prior to its use in the study. If necessary, zinc levels may be adjusted to 0.8 ppm or higher threshold by spiking with a solution of zinc chloride. The pH may be adjusted to the lower limit by using a dilute solution of hydrochloric acid. For high concentration piperacillin and tazobactam samples, use a 50 mL bag. For low concentration piperacillin and tazobactam samples, use a 150 mL bag.

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2. Reconstitute by removing 5 mL of diluent per gram of piperacillin using a syringe and needle.

3. Add the diluent withdrawn in the previous step to a vial containing the piperacillin and tazobactam product. Mix the contents to form a solution. Store this concentrate consistent with label instruction limits (e.g., 24 hours room temperature, 7 days refrigerated).

4. Return the dissolved piperacillin and tazobactam product to the diluent bag using a syringe. Mix using gentle inversions for about 30 seconds.

5. Test samples according to the methods set forth in Section 3 (Methods).

5. DATA

The data to be generated can be inserted into a table such as Table 2.

Table 2

Time = [24 hours at ambient temperature OR 7 days at 2 - 8 °C]										
Metal ion content = [high OR low]										
Mixture/Time	Potency		Diluent	Appearance		pH		HIAC		
Drug Product Concentration	Piperacillin	Tazobactam								
								≥10 μm	≥25 μm	
Low			Sterile Water							
High			Sterile Water							
Low			Sodium Chloride							
High			Sodium Chloride							
Low			D5W							
High			D5W							
Low			LRS							
High			LRS							

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6. ACCEPTANCE CRITERIA

For potency assays, each drug must meet 90 - 110 % LS (label strength). A baseline sample should be prepared for each presentation. Reconstitute lyophile, dilute in intravenous diluent and test immediately.

Visual, HIAC, and pH testing will also performed. The passing criteria for the visual test will be a clear and essentially colorless solution that is essentially free of visual particulate matter. HIAC testing will be performed on a minimum of three individually prepared bags per test point and must conform to USP <788> standards. High concentration samples must conform with the small volume injection criteria (as described in USP <788>); the low volume samples must conform to the large volume injection criteria (as described in USP <788>).