DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 15 2009

Beth Brannan
Sandoz Inc.
2555 West Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Geoffrey M. Levitt
Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101

William A. Rakoczy
Christine J. Siwik
Rakoczy Molino Mazzochi Siwik LLP
6 West Hubbard Street
Suite 500
Chicago, IL 60610

Imtiyaz Basade
Orchid Healthcare
Plot Nos. B3-B6 & B11-B14, SIPCOT Industrial Park
Irungattukottai, Kancheepuram District – 602 105
India

Re: Docket Nos. FDA-2005-P-0003, FDA-2006-P-0019, FDA-2006-P-0331, and FDA-2006-P-0391

Dear Petitioners:

This letter is a consolidated response to four citizen petitions in the dockets referred to above[1] and supplements to and comments submitted on the petitions. Three of the petitions (Sandoz Petition, Rakoczy Petition, and Orchid Petition — collectively Original Formulation Petitioners) request that the Food and Drug Administration (FDA) (1) determine that the originally approved formulation (now discontinued) of Zosyn (piperacillin sodium and tazobactam sodium for injection)[2] was not discontinued for safety or efficacy reasons; and (2) accept abbreviated new drug applications (ANDAs) for piperacillin and tazobactam for injection formulated without edetate sodium and citric acid.[3]

[1] These citizen petitions were originally assigned docket numbers 2005P-0456, 2006P-0173, 2006P-0195, and 2006P-0442. The numbers changed to FDA-2005-P-0003 (Sandoz Petition), FDA-2006-P-0019 (Wyeth Petition), FDA-2006-P-0331 (Rakoczy Petition), and FDA-2006-P-0391 (Orchid Petition), respectively, as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] In this response, *piperacillin sodium and tazobactam sodium for injection* is shortened to *piperacillin and tazobactam for injection.*

[3] The Original Formulation Petitioners request that FDA accept ANDAs for piperacillin and tazobactam for injection in the vials containing 2.25 grams (g), 3.375 g, and 4.5 g of piperacillin sodium and tazobactam

The petition submitted by Wyeth Pharmaceuticals (Wyeth) on April 25, 2006, requests that FDA require that any ANDA referencing Zosyn (1) comply with the relevant U.S. Pharmacopeia (USP) standards on particulate matter under the variety of conditions of metal ions and pH levels found in the commercial diluents permitted for use in its label; and (2) exhibit the same compatibility profile as Zosyn with respect to Lactated Ringer's Solution (LRS) and the aminoglycoside antibiotics, amikacin and gentamicin. If a generic[4] piperacillin and tazobactam for injection drug product demonstrates a compatibility profile different than that of Zosyn, Wyeth requests that FDA condition approval of that product on the ANDA applicant implementing a risk minimization action plan (RiskMAP) to keep health care practitioners aware of the differences.

FDA has carefully considered the information submitted in the petitions, supplements, comments, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, the Sandoz, Rakoczy, and Orchid Petitions are granted and the Wyeth Petition is granted in part and denied in part.

## I. BACKGROUND

### A. Zosyn

Zosyn (piperacillin and tazobactam for injection) is an injectable antibacterial combination drug product consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration. The product is principally administered in hospitals and is indicated for the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, β-lactamase-producing strains of the designated microorganisms in the specified conditions listed in the labeling. Zosyn is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic microorganisms.

Zosyn is currently available in several presentations, including (1) single-dose vials, (2) ADD-Vantage vials, (3) pharmacy bulk vials, and (4) Galaxy containers. Zosyn is in the form of a lyophilized powder when it is distributed in vials containing 2.25 g, 3.375 g and 4.5 g of piperacillin sodium and tazobactam sodium (equivalent to 2 g of piperacillin and 0.25 g of tazobactam, 3 g of piperacillin and 0.375 g of tazobactam, and 4 g of piperacillin and 0.5 g of tazobactam per vial, respectively). The 40.5 g pharmacy bulk vial contains 36 g of piperacillin and 4.5 g of tazobactam sufficient for delivery of multiple doses. In addition, Zosyn is available in the form of a frozen solution distributed in Galaxy containers.

---

sodium. In addition to those strengths, the Orchid Petition also requests that FDA accept ANDAs for piperacillin and tazobactam for injection in the 40.5 g pharmacy bulk vial.

[4] The term *generic* is used in this response to refer to drugs that are the subject of applications submitted under section 505(j) of the Act.

To use a lyophilized powdered form of Zosyn, the product is first reconstituted in the vial using a compatible reconstitution diluent, as identified in the approved product labeling.[5] The reconstituted Zosyn solution is then further diluted in a compatible intravenous solution, as identified in the approved product labeling,[6] by transferring the product to an infusion bag. After reconstitution in the vial and dilution in the infusion bag, Zosyn is administered to patients by intravenous infusion.

## B. Wyeth's Zosyn Formulations and Relevant Labeling Changes

FDA approved the original Zosyn formulation with labeling that included directions with respect to compatibility of the drug with certain products. Wyeth reformulated Zosyn (reformulated Zosyn), and the current approved product labeling continues to include specific, albeit in certain respects different, instructions with respect to compatibility. Zosyn has always been and continues to be incompatible with certain products. At the time of (and as evidenced by) FDA's approval of the products, both formulations were considered safe and effective under the labeled conditions of use. The original Zosyn formulation was not discontinued for reasons of safety or effectiveness, as discussed in section II of this response.

### *1. Original (Now Discontinued) Formulation and Labeling*

In October 1993, FDA approved the original formulation of Zosyn (new drug application (NDA) 50-684) (original Zosyn formulation). The last supplement approved before the formulation change was a labeling revision approved by FDA on June 27, 2005 (hereafter referred to as original formulation labeling). The DESCRIPTION section of the original formulation labeling stated that the product does not contain excipients or preservatives. In regard to compatibility with other products, the original formulation labeling included (in part) the following information:

- The DOSAGE AND ADMINISTRATION section stated in bold type that "[w]hen concomitant therapy with aminoglycosides is indicated, Zosyn and the aminoglycoside should be reconstituted and administered separately, due to the in vitro inactivation of the aminoglycosides with penicillin."
- The *Drug Interactions* subsection of the PRECAUTIONS section stated that "[t]he mixing of Zosyn with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside."
- The *Drug Interactions* subsection in PRECAUTIONS highlighted this effect "especially [for the aminoglycoside] tobramycin" in certain patients.

---

[5] Compatible reconstitution diluents listed in the Zosyn approved labeling are: "0.9% sodium chloride for injection, sterile water for injection, dextrose 5%, bacteriostatic saline/parabens, bacteriostatic water/parabens, bacteriostatic saline/benzyl alcohol, and bacteriostatic water/benzyl alcohol."

[6] Compatible intravenous solutions listed in the Zosyn approved labeling include: "0.9% sodium chloride for injection, sterile water for injection, dextrose 5%, dextran 6% in saline, and Lactated Ringer's Solution (compatible **only** with reformulated Zosyn containing EDTA)."

- The DOSAGE AND ADMINISTRATION section did not include Lactated Ringer's Solution (LRS) as one of the four compatible intravenous diluent solutions and included in capital, bold type letters that "Lactated Ringer's Solution is not compatible with Zosyn."
- The DOSAGE AND ADMINISTRATION section also included other specific directions for reconstitution and dilution for use, including those regarding incompatibility with other products.

After the 1993 approval, there were concerns regarding the quality of this formulation because some stability samples of the original Zosyn formulation had shown out-of-specification results on subvisible particulate matter before the expiry date. According to an article written by Wyeth's formulation development team (Wyeth authors), particulate formation was attributed to traces of nontoxic silicone oil used to lubricate the container closures and the shift toward lower pH and the formation of less soluble piperacillin acid as the product aged.[7] Wyeth submitted a supplemental application modifying the container closure and reducing the expiration dating period from the originally approved 36 months to 24 months for all Zosyn presentations, except the Galaxy containers. FDA approved the supplemental application on March 15, 2002. According to the Wyeth authors, despite these adjustments, the original Zosyn formulation continued to experience sporadic quality failures related to particulates. These particulates were isolated and were reported by the Wyeth authors to contain low solubility piperacillin dimers.[8]

*2. Current Formulation and Labeling*

In September 2005, FDA approved Wyeth's supplement for a new formulation of Zosyn (reformulated Zosyn) along with certain labeling changes. The reformulated Zosyn contains edetate disodium dihydrate (EDTA) and citric acid monohydrate. Wyeth claims that the addition of citric acid monohydrate buffers the drug product, and EDTA chelates metal ions, such as zinc. In addition, Wyeth states that the reformulated Zosyn has what it refers to as an expanded compatibility profile, including compatibility with LRS and two aminoglycoside antibacterials (i.e., gentamicin and amikacin). In regard to compatibility with other products, the current approved labeling is (in part) as follows:

- The *Drug Interactions* subsection in PRECAUTIONS states:

  > The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin have been shown to be compatible *in vitro* with reformulated Zosyn containing EDTA supplied in vials or bulk pharmacy containers in certain diluents at specific concentrations for a simultaneous Y-site infusion.

[7] Desai, N.R., Shah, S.M., Cohen, J., McLaughlin, M., and Dalal, H.R. Zosyn (piperacillin/tazobactam) reformulation: Expanded compatibility and coadministration with lactated Ringer's solutions and selected aminoglycosides. *Ther Clin Risk Manag* 4, 303-314 (2008).

[8] Desai et al.

- The DOSAGE AND ADMINISTRATION section states:

  > Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Zosyn and the aminoglycoside are recommended for separate administration. Zosyn and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated.
  >
  > In circumstances where co-administration via Y-site is necessary, reformulated Zosyn containing EDTA supplied in vials or bulk pharmacy containers is compatible for simultaneous coadministration via Y-site infusion only with [certain] aminoglycosides under [certain] conditions.

- The DOSAGE AND ADMINISTRATION section then includes a table listing the specific aminoglycosides and specific conditions of use (i.e., aminoglycoside type (gentamicin/amikacin), Zosyn dose, Zosyn diluent volume, aminoglycoside concentration range, and acceptable diluents). This section also states that the aforementioned "information does not apply to Zosyn in Galaxy containers."[9]
- The *Drug Interactions* subsection in PRECAUTIONS states that reformulated Zosyn "is not compatible with tobramycin for simultaneous coadministration via Y-site infusion."
- The DOSAGE AND ADMINISTRATION section lists LRS as one of five compatible intravenous solutions.
- The DOSAGE AND ADMINISTRATION section also includes other specific directions for reconstitution and dilution for use, including those regarding incompatibility with other products.

Both the original Zosyn formulation and reformulated Zosyn were, as Wyeth acknowledges, on the market simultaneously for some period of time (Wyeth Petition at 16). As Wyeth stated in its December 1, 2005, Dear Health Care Provider Letter, "*the dosing, safety profile, and efficacy of Zosyn has not changed.*"

## C. Today's Approval of an ANDA for Piperacillin and Tazobactam for Injection

Today, FDA approved an ANDA for piperacillin and tazobactam for injection (hereafter referred to as Orchid's generic piperacillin and tazobactam for injection product). Although Orchid's generic piperacillin and tazobactam for injection product does not include citric acid or EDTA, the generic product (like Wyeth's reformulated Zosyn) is compatible with the aminoglycosides, amikacin and gentamicin, under the labeled conditions of use.[10] Orchid's generic piperacillin and tazobactam for injection product,

---

[9] Zosyn packaged in Galaxy containers at 3.375 milligrams (mg) per 50 milliliters (mL) is not labeled for use with gentamicin due to the higher concentration of piperacillin and tazobactam. The higher concentration of piperacillin and tazobactam does not affect compatibility with LRS and amikacin.

[10] The Agency need not address in this petition response whether it would approve an ANDA for piperacillin and tazobactam for injection that does not include information to demonstrate compatibility with amikacin and/or gentamicin. The Agency intends to consider compatibility issues, as appropriate, during the ANDA review process.

like Wyeth's reformulated Zosyn, is not compatible with the aminoglycoside tobramycin, under the labeled conditions of use. The approved labeling for the Orchid product bears substantially the same aminoglycoside compatibility information as Wyeth's reformulated Zosyn. With the exception of noting incompatibility with LRS, Orchid's generic piperacillin and tazobactam for injection product has substantially the same directions for reconstitution and dilution for use as Wyeth's reformulated Zosyn. The approved labeling informs health care providers about the generic product's compatibility (or lack thereof) with aminoglycosides and LRS. Orchid's generic piperacillin and tazobactam for injection product is as safe and effective as Wyeth's reformulated Zosyn under the labeled conditions of use. As discussed below, the Agency's approval is scientifically justified, consistent with Agency precedent, and firmly supported by applicable law.

## D. ANDAs — Legal and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. An ANDA applicant does not have to submit clinical studies to demonstrate the safety and effectiveness of a drug product. Instead, an ANDA applicant relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[11] To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD as required by section 505(j)(2)(A)(iv) of the Act. In addition, an ANDA applicant must provide sufficient information to show that the generic drug product has the same active ingredient(s), dosage form, route of administration, and strength as the RLD. An ANDA applicant must also demonstrate that its product has (with certain permissible differences) the same labeling as the RLD. The Agency must approve an ANDA unless it finds, among other things, the ANDA has not provided sufficient evidence of the foregoing, or 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 (section 505(j)(4) of the Act).

The scientific premise underlying the Hatch-Waxman Amendments is that when certain aspects of the drug products (e.g., active ingredient(s), strength, dosage form, route of administration) are the same, the products may be substituted for each other. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical

[11] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (generally known as the "Orange Book").

equivalents[12] and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[13]

## II. DISCUSSION

The Original Formulation Petitioners make several requests regarding the original Zosyn formulation. Wyeth requests that FDA apply certain requirements to ANDAs for piperacillin and tazobactam for injection. The Original Formulation Petitioners and Wyeth make several arguments in support of their requests. We address the arguments below.

### A. ANDA Applicants for Piperacillin and Tazobactam for Injection Are Expected to Comply With USP General Chapter <788> for Particulates

Wyeth attributes particulate formation in the original Zosyn formulation to the diluent-promoted dimerization of piperacillin and claims that the particulate formation and batch failures were due solely to formulation (i.e., the lack of EDTA and citric acid); however, we note that the Wyeth authors appear to recognize that other factors may contribute to particulate formation.[14] Wyeth asserts that any ANDA referencing Zosyn must demonstrate compliance with USP <788> under the variety of conditions of metal ion and pH levels found in the commercial diluents permitted in the Zosyn labeling (Wyeth Petition at 10).

We agree with Wyeth insofar as any ANDA for piperacillin and tazobactam for injection (duplicating the old formulation or the new formulation) should meet the standards on particulate matter in the USP General Chapter <788>. Because of the historical concerns about particulate matter for the original Zosyn formulation, FDA intends to carefully consider particulate formation when evaluating ANDAs for piperacillin and tazobactam for injection. We have considered the basic scientific principles described in Wyeth's protocol[15] regarding the particulate matter effect of low pH and high zinc ion concentration. We do not intend to use Wyeth's specific protocol in evaluating ANDAs for piperacillin and tazobactam for injection because ANDA applicants, like NDA applicants, can have different manufacturing processes and flexibility in evaluating and

---

[12] Drug products are considered pharmaceutical equivalents if they contain the same active ingredient, are of the same dosage form, route of administration, and are identical in strength or concentration. Orange Book at vi.

[13] FDA classifies as therapeutic equivalents products that (1) are approved as safe and effective; (2) are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) are bioequivalent; (4) are adequately labeled; and (5) are manufactured in compliance with Current Good Manufacturing Practice regulations. Orange Book at vii.

[14] Desai et al.

[15] See appendix of the Wyeth Petition.

demonstrating the robustness of the formulations in relation to particulate formation is appropriate. Commercial diluents commonly used to reconstitute and administer Zosyn may have varying pH levels and zinc ion concentrations.

When reviewing ANDAs for piperacillin and tazobactam for injection, FDA intends to consider the variability of these diluent quality attributes in the context of their potential to affect particulate formation in the drug product. In addition, FDA expects that for ANDAs duplicating the original Zosyn formulation, applicants will test for particulate formation under the conditions-of-product-use described in the labeling, including use with different diluents. During the ANDA review process, ANDA applicants must demonstrate that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.[16]

On June 4, 2009, Wyeth submitted a supplement to its petition to inform the Agency about a "new compendial standard" governing piperacillin/tazobactam products.[17] The "new standard" is an update of the USP Piperacillin and Tazobactam for Injection monograph that is proposed to become official on December 1, 2009.[18] The update includes a test for particulate matter formation in low pH solutions in the presence of zinc ions.[19] We believe that the proposed particulate matter test is inconsistent with the particulate matter standards for other USP monographs.[20] We currently do not require NDA or ANDA applicants to comply with this proposed monograph. If this monograph does become final, we would expect both NDAs and ANDAs for piperacillin and tazobactam for injection to comply with the new standard.

## B. Original Zosyn Formulation Was Not Discontinued for Reasons of Safety or Efficacy

The Original Formulation Petitioners request that FDA (1) determine that the originally approved formulation (now discontinued) of Zosyn (piperacillin and tazobactam for injection) was not discontinued for safety or efficacy reasons; and (2) accept ANDAs for piperacillin and tazobactam for injection, 2.25 g, 3.375 g, and 4.5 g, without edetate sodium and citric acid (Sandoz Petition at 1-2, Rakoczy Petition at 1-2, Orchid Petition at 1). In addition to requesting a safety and efficacy determination for the aforementioned

---

[16] Section 505(j)(4) of the Act.

[17] FDA-2006-P-0019-0012.

[18] USP32-NF27 Supplement Number 2 at 4275.

[19] Specifically, the proposed monograph requires product compliance with particulate matter levels as outlined in USP <788> for 5% dextrose solution at pH 3.2-3.5 spiked with 0.8 parts per million zinc chloride.

[20] Monograph tests are meant to establish an appropriate set of routine test criteria that describe the product and establish minimum quality standards. Although in-use studies such as those used to monitor possible extremes of diluent conditions may be appropriate during product development, these are generally not considered to be appropriate routine tests.

strengths, the Orchid Petition also requests that FDA accept ANDAs for piperacillin and tazobactam for injection in the 40.5 g pharmacy bulk vial. In a supplement dated March 1, 2006, Sandoz presents information to support its view that Zosyn without EDTA and citric acid monohydrate is stable in solutions for infusion (Sandoz Petition, Supplement at 2).[21]

Wyeth attributes the formation of particulates to the presence of metal ions (such as zinc) and downward shifts in pH as the product aged. Wyeth asserts that reformulation of Zosyn with the metal chelator EDTA and the buffer citric acid monohydrate controls metal ion concentration and product pH, thereby inhibiting particulate formation and ensuring compliance with particulate matter levels outlined in USP <788> under all foreseeable use conditions (Wyeth Petition at 8).

We have determined that the original Zosyn formulation was safe and effective for the labeled conditions of use and was not withdrawn from the market for reasons of safety or efficacy. Generally, product stability depends on multiple factors, such as formulation, storage temperature, storage duration, container-closure systems, and manufacturing processes. Accordingly, it is possible that particulate problems with the original Zosyn formulation that persisted after the container closure was modified and the expiry period was reduced may have been related to manufacturing or other issues. FDA is not persuaded that Zosyn particulate matter levels were brought into USP <788> compliance by formulation adjustments alone.

Furthermore, based on the Agency's search of adverse event reporting databases and other available information, there does not appear to be evidence of particulate-related adverse effects in postmarketing or literature reports concerning the original Zosyn formulation. Wyeth marketed the original Zosyn formulation for nearly 13 years. The original Zosyn formulation labeling included information regarding aminoglycosides and LRS as well as other directions for reconstitution and dilution for use sufficient to alert health care providers of compatibility issues associated with the product. Both the original Zosyn formulation and reformulated Zosyn were on the market simultaneously for some period of time. Wyeth also states that "the nature and level of the particulates did not present a clinically significant safety concern" (January 20, 2006, Wyeth Comment to Sandoz Petition). As Wyeth stated (post-Zosyn reformulation) in its December 1, 2005, Dear Health Care Provider Letter, "*the dosing, safety profile, and efficacy of Zosyn has not changed.*" The Agency concludes that the original Zosyn formulation was and continues to be safe and effective under the labeled conditions of use, and was not discontinued for reasons of safety or effectiveness.

### C. FDA May Approve ANDAs for Piperacillin and Tazobactam for Injection Duplicating the Original Zosyn Formulation

In its petition, Wyeth states that FDA regulations require generic drug products to duplicate the currently marketed reformulated Zosyn (Wyeth Petition at 12). Wyeth states that FDA regulations require that a generic injectable drug product must generally

[21] FDA-2005-P-0003-0007.

contain the same inactive ingredients as the reference drug (Wyeth Petition at 12). Wyeth states that differences in preservatives, buffers, and antioxidants are permitted, but the generic drug applicant must demonstrate that such differences do not affect the safety or efficacy of the proposed drug (Wyeth Petition at 12). Wyeth states that other differences in chemical composition are not permitted.

The Act (section 505(j)(4)(H)) provides that FDA must approve an ANDA unless:

> information submitted in the [ANDA] or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

In general, an ANDA may have different inactive ingredients from the RLD as long as the ANDA demonstrates that the different inactive ingredients do not affect the safety or efficacy of the proposed drug product (21 CFR 314.94(a)(9)(ii)). However, for ANDAs for parenteral drug products, the only differences in excipients that are routinely permitted are changes in a preservative, a buffer, or an antioxidant. FDA's regulation in § 314.94(a)(9)(iii) concerning the content and format of an ANDA states the following:

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant. . . . However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The corresponding provision that addresses the refusal to approve an ANDA, 21 CFR 314.127(a)(8)(ii)(B), provides the following:

> FDA will consider an active ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the [ANDA] unless it contains the same inactive ingredients, other than preservatives, buffers, antioxidants, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

The regulations governing inactive ingredients were issued to address particular safety concerns posed by parenteral drug products. In addressing comments on proposed § 314.127 regarding changes in preservatives, buffers, and antioxidants, the Agency noted in the preamble of the final rule that under the statute, the inquiry is whether these inactive ingredients are "safe under the conditions prescribed, recommended, or

suggested in the labeling" and that the regulation "reflects this concern, which is particularly acute for parenteral drug products" (57 FR 17950 at 17970; April 28, 1992).[22]

When an ANDA applicant seeks approval for a parenteral formulation that is the same as that previously marketed by the innovator, FDA has determined that, in appropriate circumstances, it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same as those in the reference listed drug (except for preservatives, buffers, and antioxidants). FDA may not waive a statutory requirement for approval of an ANDA. Thus, differences between the ANDA and RLD formulations that are shown to be unsafe based on available information will preclude ANDA approval (section 505(j)(4)(H) of the Act). The Agency may rely on § 314.99(b) (21 CFR 314.99(b)) to grant a waiver of the regulation requirement — that the ANDA and NDA formulations contain the same inactive ingredients in the same concentrations as the RLD, with limited exceptions for preservatives, buffers, and antioxidants — insofar as the statutory requirement regarding safety of inactive ingredients has been met. This waiver provision states that "[a]n applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under § 314.90."[23]

FDA may approve ANDAs for piperacillin and tazobactam for injection duplicating the original Zosyn formulation. Such ANDAs would differ from the reformulated Zosyn with respect to the inactive ingredient EDTA, which is not a preservative, buffer, or antioxidant.[24] Here, experience with Wyeth's original Zosyn formulation and FDA's recent analysis has shown that the inactive ingredients in the ANDA for piperacillin and tazobactam for injection duplicating the original Zosyn formulation are safe. As discussed above, FDA has determined that the original Zosyn formulation was safe and effective under the labeled conditions of use and was not discontinued for reasons of safety or effectiveness. (We also note that ANDAs for piperacillin and tazobactam for injection would have appropriate labeling to assure the safe use of the drug, as discussed

---

[22] The regulations address the use of excipients that were not expected to be adequately addressed in the ANDA context (e.g., unfamiliar excipients, or excipients of a type more likely to raise safety concerns for parenteral drugs). It seems apparent that neither FDA nor comments on the proposed rule anticipated that an ANDA applicant might seek approval to market a previous formulation of a drug product that FDA had approved as safe.

[23] Section 314.99 addresses the waiver of certain submission requirements described in § 314.94. Waiver of the parallel requirements described in § 314.127 for refusing to approve an ANDA is not explicitly stated. However, FDA interprets waiver of the submission requirement to carry with it the implicit waiver of the approval requirement. The statement in § 314.99 that an applicant may ask FDA to waive "*any* requirement that applies to the applicant" under § 314.94 would be meaningless with respect to the provisions of § 314.94 that have parallels in § 314.127 unless waiver of a submission requirement under § 314.94 permitted waiver of the corresponding approval requirement.

[24] We note that the difference in buffer (i.e., citric acid monohydrate) would not affect the safety or effectiveness of the proposed product and would be expressly permitted by §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B).

further below.) Because 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. This conclusion is supported by FDA regulations, is justified by the science, is consistent with the statutory requirements for ANDA approval, and is consistent with the Agency's previous decisions.[25] Therefore, ANDAs for piperacillin and tazobactam for injection products proposing the same formulation as the original Zosyn formulation may be approved as long as the ANDA meets the other statutory requirements for approval.

### D. Generic Piperacillin and Tazobactam for Injection Is Safe and Effective Under the Labeled Conditions of Use

Wyeth states that FDA should not approve ANDAs for piperacillin and tazobactam for injection unless the drug products exhibit the same compatibility profile as that of Zosyn, particularly with respect to LRS and the aminoglycoside antibacterials amikacin and gentamicin (Wyeth Petition at 10). Wyeth adds that even if a generic product is robust enough to satisfy the USP <788> particulate test, the generic product may exhibit a compatibility profile different from Zosyn's with respect to LRS, amikacin, and gentamicin (Wyeth Petition at 10). Furthermore, Wyeth argues that a generic product that exhibits a compatibility profile different from Zosyn's would create public health risks because a generic product that is not compatible with LRS, amikacin, and gentamicin — and thus cannot be used interchangeably with Zosyn — could cause confusion among practitioners (Wyeth Petition at 11).

The Act requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[26]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR

[25] *See, e.g.*, March 25, 2005, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to Molly Rapp and Anthony Celeste, Docket Nos. 2001P-0574 and 2005P-0061.

[26] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

> 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . . 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 accorded exclusivity under section 505(j)(4)(D) of the [A]ct.)[27] (emphasis added)

The parallel provision for refusal to approve an ANDA based on labeling changes can be found at section 314.127(a)(8)(7).

Orchid's generic piperacillin and tazobactam for injection product duplicates the original Zosyn formulation and the labeling reflects the difference in formulation between the generic drug product and reformulated Zosyn — a difference in labeling expressly permitted under the Act and regulations. Consequently, Orchid's generic piperacillin and tazobactam for injection product labeling includes appropriate information to inform health care providers about the generic drug product's compatibility with other products, such as aminoglycosides and LRS, as discussed further below.

*1. Aminoglycosides*

Aminoglycosides are antibacterial products used primarily to treat infections caused by aerobic gram-negative bacteria via the inhibition of protein synthesis. These natural products or semisynthetic compounds contain amino sugars linked to an aminocyclitol ring by glycosidic bonds.

Coadministration of certain aminoglycosides with piperacillin/tazobactam products is indicated for diseases such as *Pseudomonas aeruginosa* pneumonia where broad coverage against treatment-resistant organisms is necessary. Several compatibility studies reported in the literature have shown, however, that β-lactam antibacterial drugs such as piperacillin may inactivate aminoglycosides. In vitro evidence suggests that the inactivation mechanism involves the nucleophilic reaction of the aminoglycoside amino group with the β-lactam ring, resulting in the formation of a biologically inactive amide.

Several studies demonstrate that when β–lactam antibacterial products (including piperacillin) are combined with aminoglycosides, diminished activity is a concern.[28] The

---

[27] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

[28] Glew, R.H. and Pavuk, R.A. Stability of gentamicin, tobramycin, and amikacin in combination with four beta-lactam antibiotics. *Antimicrob Agents Chemother* 24, 474-477 (1983); Pickering, L.K. and Rutherford, I. Effect of concentration and time upon inactivation of tobramycin, gentamicin, netilmicin and amikacin by azlocillin, carbenicillin, mecillinam, mezlocillin and piperacillin. *J Pharmacol Exp Ther* 217, 345-349 (1981).

studies also show, however, that aminoglycoside inactivation is not instantaneous and may depend on several variables. The extent of inactivation may depend on the specific β–lactam[29] and aminoglycoside used, as well as on drug concentration, contact time, and temperature, among other factors.

The current approved labeling for reformulated Zosyn vials, ADD-Vantage vials, bulk pharmacy vials, and two of the Galaxy presentations (2.25 g per 50 milliliters (mL) and 4.5 g per 100 mL) is similar. The *Drug Interactions* subsection of the PRECAUTIONS section in the current approved labeling states, in part:

> The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin have been shown to be compatible *in vitro* with reformulated Zosyn containing EDTA ... in certain diluents at specific concentrations for a simultaneous Y-site infusion. (See DOSAGE AND ADMINISTRATION) Reformulated Zosyn containing EDTA is not compatible with tobramycin for simultaneous coadministration via Y-site infusion.

Furthermore, the DOSAGE AND ADMINISTRATION section of the current approved labeling states, in part:

> Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Zosyn and the aminoglycoside are recommended for separate administration. Zosyn and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated.

This section of the current approved labeling includes a list of diluents and conditions acceptable for the use of reformulated Zosyn in combination with the specific aminoglycosides amikacin and gentamicin. The section then states:

> Zosyn is not compatible with tobramycin for simultaneous coadministration via Y-site infusion. Compatibility of Zosyn with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of Zosyn listed have been established as compatible for coadministration via Y-site infusion. Simultaneous coadministration via Y-site infusion in any manner other than listed may result in inactivation of the aminoglycoside by Zosyn.[30]

We have been unable to identify, in the NDA for the original Zosyn formulation (NDA 50-684), data submitted by Wyeth indicating that the drug product was incompatible with the aminoglycosides amikacin and gentamicin. The labeling statement advising against

---

[29] For example, piperacillin causes less aminoglycoside inactivation than more reactive β–lactam carbenicillin.

[30] The reformulated Zosyn product labeling states that the product in Galaxy containers at 3.375 g per 50 mL is not compatible with gentamicin for coadministration via a Y-site because of high concentrations of piperacillin and tazobactam.

use of the original Zosyn formulation with aminoglycosides appears to be based upon general knowledge regarding β–lactam reactivity and data concerning β-lactam inactivation of aminoglycosides reported in the literature.[31]

Data submitted by Wyeth in support of the Zosyn reformulation showed little inactivation of amikacin or gentamicin in vitro by reformulated Zosyn when the drugs were mixed under conditions that simulate a Y-site administration system with a 30-minute infusion time.[32] In such a system, the contact time between the aminoglycosides and reformulated Zosyn being administered is estimated to be about 15 minutes and not exceeding 60 minutes.[33] Because no significant inactivation of amikacin or gentamicin was observed under these conditions, the labeling for reformulated Zosyn provides for coadministration with amikacin or gentamicin via a Y-site or multiple port infusion system under certain very narrow conditions.[34] We note that Wyeth's reformulated Zosyn remains incompatible with tobramycin (an aminoglycoside). For this reason, current approved labeling for reformulated Zosyn still cautions against administration with aminoglycosides other than amikacin and gentamicin and specifically cautions about incompatibility with tobramycin. We also note that Wyeth did not report comparative results for Y-site administration of aminoglycosides mixed with the original Zosyn formulation. Therefore, there are no data to support Wyeth's assertion that reformulated Zosyn necessarily confers a significant advantage over the original Zosyn formulation in terms of amikacin and gentamicin compatibility.

Orchid submitted in its ANDA for generic piperacillin and tazobactam for injection (duplicating the original Zosyn formulation) data to show that under the condition of use for which it is labeled, Orchid's generic product, like Wyeth's reformulated Zosyn, exhibits (1) compatibility with amikacin and gentamicin and (2) incompatibility with tobramycin. Specifically, Orchid took into account potential diluent variability (pH and metal ion concentration) under labeled conditions of use and compared its products to reformulated Zosyn in side-by-side evaluations of piperacillin/tazobactam potency, aminoglycoside potency, and particulate formation.

Accordingly, the labeling for Orchid's generic piperacillin and tazobactam for injection product is substantially the same as the labeling for Wyeth's reformulated Zosyn with respect to information regarding compatibility with the aminoglycosides amikacin and gentamicin.[35]

---

[31] Flournoy, D.J. Factors influencing the inactivation of aminoglycosides by beta-lactams. *Methods Find Exp Clin Pharmacol* 1, 233-238 (1979).

[32] The current Zosyn labeling states that intravenous infusion should take place over 30 minutes.

[33] Desai et al.

[34] The Zosyn labeling lists diluents and specific amikacin/gentamicin concentration ranges that are acceptable.

[35] Like the labeling for all Zosyn products (original and reformulated), the approved labeling for Orchid's generic piperacillin and tazobactam for injection cautions about incompatibility with tobramycin.