



April 27, 2007

Jennie C. Butler
Director
Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Ref: Docket 2005P-0456/CP1

Dear Ms. Butler:

Abraxis Pharmaceutical Products, a Division of Abraxis Bioscience Inc., is submitting the following comments in response to Wyeth Pharmaceuticals ("Wyeth") letter dated January 20, 2006 in which Wyeth is requesting the Food & Drug Administration (FDA) to deny the Sandoz Inc. ("Sandoz") Citizen Petition for the acceptance of Abbreviated New Drug Application (ANDA) submissions using the discontinued formulation of Zosyn® (piperacillin-tazobactam).

Also within the January 20, 2006 document, Wyeth further requests that if the *Agency* does accept ANDA(s) for filing based on the discontinued formulation of Zosyn® (piperacillin-tazobactam), FDA should only approve ANDA(s) for the proposed products which meet the following two criteria:

1. The generic product should comply with the current United States Pharmacopeia standard (USP <788>) for particulate matter under actual use conditions.
2. The proposed drug product applicant should be required to implement an effective risk minimization action plan due to significant differences in the discontinued Zosyn® formulation and the reformulated formulation.

Pursuant to Wyeth's refutation to the Citizens Petition, Abraxis Pharmaceutical Products further endorses Sandoz's request that FDA proceed with the determination that the discontinued formulation of Zosyn® (piperacillin and tazobactam for injection) packaged in convention and ADD-Vantage 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

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0.5 g of tazobactam per vial, respectively, was not discontinued for safety and efficacy reasons based on the following rationale provided in response to Wyeth's proposed grounds for denial.

1. The generic product should comply with the current United States Pharmacopeia standard (USP <788>) for particulate matter under actual use conditions.

Abraxis Pharmaceutical Products would like to state that per the current compendial and regulatory requirements, all small volume parenteral drug products must meet the particulate matter specifications of not more than 6000 for particles $\geq 10\mu\text{m}$ and not more than 600 for particles $\geq 25\mu\text{m}$ to obtain FDA approval for a generic product. For powder fill products like Zosyn®, the USP <788> test is performed by dissolving the contents of the drug product vial in a compatible diluent followed by analyzing the reconstituted solution using the instruments mentioned in the compedia. Since the particulate matter testing is routinely performed on all drug products intended for parenteral use, Wyeth's request to the FDA does not pose any hurdle for any generic ANDA applicant seeking approval for a generic piperacillin-tazobactam injection drug product.

The discontinued formulation of Zosyn® (NDA 50-684) was approved by the FDA on October 22, 1993. The discontinued drug product formulation of Zosyn® was described in Wyeth's package insert as a cryodesiccated powder of piperacillin and tazobactam, as their sodium salts, packaged in a glass vial. In order to administer Zosyn® to a patient, the drug product has to be diluted with a minimum of 5 mL of a compatible diluent. This reconstituted solution containing the drug product should be further diluted using 50 mL to 150 mL in a compatible intravenous diluent solution.

Based on the aforementioned dilution of the drug product injection in an aqueous solution and in accordance with the basic principles of physical chemistry, it is highly unlikely that the dissociated sodium salt of the piperacillin ion in an aqueous environment can form insoluble piperacillin monohydrate particles in solution.

Additionally, chemical synthesis of piperacillin is well documented in a scientific publication over twenty years ago¹. According to the research paper piperacillin is produced by a reaction between ampicillin and 4-ethyl-2,3-doxo-1-piperazinecarbonyl chloride. Subsequently, the piperacillin moiety is converted to a sodium salt to enhance the solubility of piperacillin moiety in an aqueous solution. Therefore, it is very improbable that crystallization of piperacillin to form trace amounts of piperacillin monohydrate particles can occur in a 50 to 150 mL aqueous solution containing numerous cations and anions.

Ultimately, in accordance with the compendial requirements for injectable drug products, all small volume parenteral drug products must meet the particulate matter specifications of not more than 6000 for particles $\geq 10\mu\text{m}$ and not more than 600 for particles $\geq 25\mu\text{m}$ to obtain FDA approval, and there is no scientific explanation that would signify that piperacillin-tazobactam products without EDTA and/or citric acid monohydrate would not have adequate particulate matter content.

2. The Proposed Drug Product applicant should be required to implement an effective risk minimization action plan due to significant differences in the discontinued Zosyn® formulation and the reformulated formulation.

The reformulated Zosyn® formulation contains EDTA and citric acid as excipients. In accordance with 21 CFR 314.94 (9)(iii), a different antioxidant, buffer or preservative can be used in a proposed drug product intended for parenteral use. Since citric acid acts as a buffer in an aqueous solution and EDTA is also known to possess antimicrobial properties and has been used as a preservative in a FDA approved parenteral product (Diprivan®), the two listed ingredients present in the reformulated Zosyn drug product can be substituted and/or eliminated in a proposed drug product.

Therefore, absence or substitution of the two aforementioned excipients in a proposed drug product should not have any impact on the therapeutic equivalence of the generic drug product using the reformulated Zosyn® as a RLD. Additionally, a bioequivalence waiver can be requested for an ANDA for a generic piperacillin-tazobactam injection since the absence of the two inactive ingredients, namely citric acid and EDTA, present in the reformulated Zosyn® have no pronounced therapeutic effect.

Furthermore, Wyeth's comprehensive and detailed communication program, in which the Zosyn® sales representatives assisted practitioners to differentiate between the two formulations during the concurrently availability of both Zosyn® formulations in the market, will allow for continued minimized medical error and protection of patient safety if generic piperacillin-tazobactam drug product is allowed to enter the market. Generic drug products have identical labeling and similar packaging as that of the innovator. The new label and redesigned packaging for the reformulated Zosyn® (yellow background) will allow healthcare providers to easily decipher between the reformulated Zosyn® and discontinued Zosyn®. Wyeth has already communicated the differences between the discontinued Zosyn® and Reformulated Zosyn® to practitioners, therefore Abraxis Pharmaceutical Products does not see the relevance of any further risk management plans.

In addition to the above facts, Wyeth's request for implementation of an effective risk management plan by the generic drug manufacture to the FDA should be disregarded based on the fact that the presence or absence of the two inactive ingredients in the piperacillin-tazobactam drug product injection has no clinically observed therapeutic effect, and, thus, do not represent a significant variation in the drug product.

Based on Wyeth's dispute, the formulation for Zosyn® was revised as a precaution, not as a result of safety or efficacy concerns. The Agency's concerns with Wyeth's Protonix® IV (pantoprazole sodium) for Injection drug product, resulted in Wyeth's investigation initiation and subsequent reformulation of Protonix®. According to Wyeth, *"Because Zosyn® and Protonix® IV had similar particulate issues, Wyeth expected that FDA would, at some point, require it to reformulate Zosyn® just as FDA had required the reformulation of Protonix® IV, even though the initial particulate issue with Zosyn® had been resolved."*

Additionally, within the January 20, 2006 Letter of Dispute, Wyeth clearly stated the following:

*"In 2000 and 2001, Wyeth discovered unexpected levels of subvisible particulate matter in certain batches of Zosyn®, and FDA indicated that the levels should be reduced. Wyeth immediately began investigations to control particulate levels in the product. Wyeth also committed to FDA that it would study the nature and cause of the particulate formation in order to resolve the issue.....The silicone particles were eliminated by incorporating new manufacturing processes that rendered a silicone oil lubricant unnecessary. **The nature and level of the particulates did not present a clinically significant safety concern. Steps taken by Wyeth, however, eliminated the excess particulate matter to FDA's satisfaction.**"*

It is fairly apparent from Wyeth's letter sent to the FDA that the older formulation of Zosyn® was not discontinued for safety or efficacy reasons.

Conclusion

Based on the aforementioned scientific facts and in the spirit of the federal regulations governing the generic drug approval process, Abraxis Pharmaceutical Products humbly requests the Commissioner of the FDA to publish a Federal Register Notice stating that the discontinued formulation of Zosyn® was not withdrawn from the market due to safety or efficacy issues.

Sincerely,



Shahid Ahmed
Vice President, Regulatory Affairs

¹ Journal of Pharmaceutical Sciences Vol 73, No.4, April 1984.