

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

0708 '06 MAY -4 P1:45

Wyeth

May 4, 2006

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

Re: Docket 2005P-0456

Dear Sir or Madam:

On November 1, 2005, Sandoz Inc. ("Sandoz") filed a citizen petition requesting that the Food and Drug Administration ("FDA") determine that a discontinued formulation of Zosyn® (piperacillin and tazobactam for injection) was not discontinued for reasons of safety or effectiveness. The petition also requested that FDA accept Sandoz's abbreviated new drug applications for products duplicating the discontinued Zosyn® formulation. On January 20, 2006, Wyeth filed comments in response to the Sandoz citizen petition (the "Response"). Sandoz then filed a supplement to its citizen petition on March 1, 2006 (the "Sandoz Supplement"). Wyeth hereby responds to the Sandoz Supplement.

I. STABILITY INFORMATION INCLUDED IN THE SANDOZ SUPPLEMENT DOES NOT ADDRESS PARTICULATE CONCERNS RAISED IN THE RESPONSE

One of the points articulated by Wyeth in the Response is that any generic product referencing either the original or reformulated versions of Zosyn® should be rigorously tested to ensure compliance with U.S. Pharmacopeia standards on particulate matter in injectable drugs set forth in General Chapter <788>.¹ Wyeth's position in the Response is that a product's compliance with USP <788> can only be demonstrated by testing the product under all possible use conditions permitted in the product's labeling. Such testing is the only way to account for the varying pH and metal ion levels existing in clinical practice that affect particulate formation.

The Sandoz Supplement states that the scientific literature clearly indicates that the discontinued Zosyn® formulation, piperacillin and tazobactam without edetate disodium dihydrate ("EDTA") and citric acid monohydrate, is stable in solution.

¹ USP <788> "Particulate Matter for Injections."

Wyeth does not dispute this point, but disputes the presumption in the Sandoz Supplement that a product with a demonstrated stability record need not independently satisfy USP <788>. While chemical stability is a basic requirement with respect to the development of injectable drugs, stability data alone are by no means an indication of compliance with particulate standards. It is entirely possible for a drug product to demonstrate sufficient stability for clinical applications and simultaneously fail USP <788> particulate standards.

It is easy to illustrate through an example that a product can have excess particulate matter but still readily comply with stability requirements. Consider, for example, a 4.5 gram dose of a combination piperacillin/tazobactam product (4.0 grams piperacillin, 0.5 gram tazobactam). USP <788> requires that the reconstituted drug contain no more than 6000 particulates greater than $10\mu\text{m}$ in diameter and no more than 600 particulates greater than $25\mu\text{m}$ in diameter, per 100 milliliters of solution. Suppose that the product exceeds both of the USP particulate limits, yielding 7000 particulates $10\mu\text{m}$ in size and 700 particulates $25\mu\text{m}$ in size. Exceeding the USP particulate limits even by this amount, however, results in a loss of only approximately 16.9 micrograms (16.9×10^{-6} gram) of piperacillin (see calculation set forth in Appendix I).

A loss of 16.9 micrograms of piperacillin would be undetectable by a high-performance liquid chromatography (“HPLC”) assay with a typical $\pm 1.0\%$ standard deviation (uncertainty error). In fact, the HPLC assay would need to be several thousand times more precise in order to detect losses of piperacillin resulting from excess particulate formation.² Thus, measuring the amount of piperacillin in a stability test provides no useful information about compliance with the standards on particulate matter.

II. WYETH’S “DEAR HEALTH CARE PROVIDER” LETTER IS NOT EVIDENCE THAT A GENERIC PRODUCT BASED ON THE DISCONTINUED FORMULATION OF ZOSYN® SHOULD BE APPROVED

The Sandoz Supplement references a “Dear Health Care Provider” letter distributed by Wyeth in December 2005. The letter notified health care practitioners that FDA had approved the reformulated version of Zosyn® and

² An HPLC assay with an error rate of $\pm 1\%$ standard deviation (“sd”) when applied to a 4 gram sample of piperacillin yields a $\pm 0.04 \times 2.3 \text{ sd} = (9.2 \times 10^{-2})$ gram margin of error. In order to detect a loss of 16.9×10^{-6} gram, the HPLC assay would have to be 5.4×10^3 , or about 5 thousand, times more powerful.

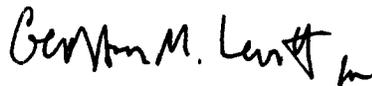
informed them of the relevant differences between the reformulated version and the original version. In particular, the letter highlighted the expanded compatibility of the reformulated product with Lactated Ringer's Solution and two aminoglycoside antibiotics, amikacin and gentamicin. The letter also reassured practitioners that the dosing, safety profile, and efficacy of the product had not changed.

The Sandoz Supplement seems to suggest that because there are no differences in dosing, safety, or efficacy between the original and reformulated versions of Zosyn®, a generic product duplicating the original version presents no issues. This is incorrect, however, due to the reformulated product's expanded compatibility profile and its ability to comply with USP <788> particulate requirements. Because of the reformulated product's expanded compatibility profile, the simultaneous presence of reformulated Zosyn® and a generic product duplicating the original formulation of Zosyn® raises significant public health risks.³ The Sandoz Supplement did not address these concerns.

III. CONCLUSION

For the reasons stated above and in the Response, Sandoz's citizen petition requesting that FDA accept its abbreviated new drug applications for products duplicating the original Zosyn® formulation should be denied.

Sincerely,



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

³ See Citizen Petition filed by Wyeth on April 25, 2006 (Docket No. 2006P-0173).

APPENDIX I**IF**

A 4 gram sample of piperacillin (density = 2 g/cm³) yields 7,000 particles 10µm in size and 700 particles 25µm in size.

THEN

1. Volume of one particle (assuming spherical shape with a diameter R) = $(4/3) \times \pi \times R^3$

$$\text{Volume of one 10}\mu\text{m particle} = (4/3) \times \pi \times (0.0010/2)^3 = 5.23 \times 10^{-10} \text{ cm}^3$$

$$\text{Volume of one 25}\mu\text{m particle} = (4/3) \times \pi \times (0.0025/2)^3 = 8.18 \times 10^{-9} \text{ cm}^3$$

2. Volume of all particles = number of all particles x volume of one particle

$$\text{Volume of all 10}\mu\text{m particles} = 7000 \times 5.23 \times 10^{-10} \text{ cm}^3 = 3.66 \times 10^{-6} \text{ cm}^3$$

$$\text{Volume of all 25}\mu\text{m particles} = 700 \times 8.18 \times 10^{-9} \text{ cm}^3 = 5.72 \times 10^{-6} \text{ cm}^3$$

3. Weight of all particles = density of particles x volume of all particles

$$\text{Weight of all 10}\mu\text{m particles} = 1.8 \text{ g/cm}^3 \times 3.66 \times 10^{-6} \text{ cm}^3 = 6.59 \times 10^{-6} \text{ g}$$

$$\text{Weight of all 25}\mu\text{m particles} = 1.8 \text{ g/cm}^3 \times 5.72 \times 10^{-6} \text{ cm}^3 = 10.3 \times 10^{-6} \text{ g}$$

4. Total weight of all 10µm and 25µm particles = weight of 10µm particles + weight of 25µm particles

$$\text{Weight of all particles} = 6.59 \times 10^{-6} \text{ g} + 10.3 \times 10^{-6} \text{ g} = 16.9 \times 10^{-6} \text{ g}$$

5. Detection of difference limit = 2.3 x 4g x 1% = 9.2 x 10⁻² g.

6. Number of times all particles would need to weight to meet detection limit:

$$\frac{9.2 \times 10^{-2} \text{ g}}{16.9 \times 10^{-6} \text{ g}} = 5445 = 5.445 \times 10^3$$