Orchid
HEALTHCARE
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Date: October 23, 2006

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

1721 '06 OCT 27 P3:

CITIZEN PETITION

Dear Sir or Madam:

Orchid Healthcare, a Division of Orchid Chemicals & Pharmaceuticals Ltd. (Orchid), submits this petition in quadruplicate, pursuant to Section 505 (j)(2)(c) of the Federal Food, Drug and Cosmetic Act, and in accordance with the U.S. Food and Drug Administration regulations at 21 C.F.R. § 10.30.

A. Action Requested

Orchid respectfully requests that FDA issue a determination that Wyeth Pharmaceuticals, Inc. (Wyeth) discontinued its previously-approved formulation of the Reference Listed Drug (RLD) Zosyn® (piperacillin and tazobactam for injection), 40.5 gram pharmacy bulk vial, for reasons unrelated to safety and effectiveness. This Petition also references two separate citizen petitions requesting that FDA issue the same determination with respect to the previously-approved formulation of Zosyn® packaged in vials containing 2.25 grams, 3.375 grams and 4.5 grams of piperacillin sodium and tazobactam sodium. Petitioner requests that FDA, pursuant to the determination requested in this and the cross-referenced citizen petitions, accept Abbreviated New Drug Applications (ANDAs) for piperacillin and tazobactam for injection, 40.5 gram pharmacy bulk vial, equivalent to 36 grams of piperacillin and 4.5 grams of tazobactam sufficient for delivery of multiple doses, and ANDAs for piperacillin and tazobactam for injection, packaged in vials containing 2.25 grams, 3.375 grams and 4.5 grams of piperacillin sodium and tazobactam sodium in each case without edetate disodium dihydrate (EDTA) and citric acid monohydrate.

B. Statement of Grounds

Wyeth first obtained approval of a New Drug Application (NDA) for Zosyn® in 1993 (NDA 50-684). Wyeth's patent for this original formulation of the product will expire in February 2007. On September 30, 2005, Wyeth obtained approval of a reformulated version of Zosyn® (NDA 50-684/045). Reformulated Zosyn® contains two patented inactive ingredients – edetate disodium dihyrdrate ("EDTA") and citric acid monohydrate – that were not contained in the previously-approved formulation.

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Wyeth supplies Zosyn® in a conventional vials containing 2.25 grams, 3.375 grams and 4.5 grams of piperacillin sodium and tazobactam sodium. It also supplies the product in a 40.5 gram pharmacy bulk vial, equivalent to 36 grams of piperacillin and 4.5 grams of tazobactam sufficient for delivery of multiple doses.[1] Following Wyeth's receipt of approval for its supplemental NDA covering the new formulation of Zosyn®, two separate parties filed citizen petitions requesting that the FDA issue a determination that Wyeth withdrew the previously-approved formulation of Zosyn®, packaged in vials containing 2.25 grams, 3.375 grams and 4.5 grams of piperacillin sodium and tazobactam sodium, from the market for reasons other than safety and efficacy.[2] These citizen petitions also request that FDA accept ANDAs for the previously-approved version of Zosyn® in the package forms cited in those petition. Wyeth has challenged the requests made in these petitions in three separate filings to the citizen petition dockets.

In this citizen petition, Orchid requests that FDA issue a determination that the original formulation of Zosyn® (piperacillin and tazobactam for injection) packaged in 40.5 g pharmacy bulk vial was not withdrawn by Wyeth for reasons of safety and efficacy, and that FDA accept ANDAs for generic Piperacillin and Tazobactam for Injection, without the inactive ingredients EDTA and citric acid monohydrate, in this package form. As information submitted to the dockets for the citizen petitions requesting a similar determination from FDA for the other package forms of Zosyn®, Wyeth reformulated the product to include the inactive ingredients EDTA and citric acid monohydrate in order to limit particulate formation in the product. Wyeth has explicitly stated that the level of particulates in the original formulation – the sole articulated reason for the reformulation – "did not present a clinically significant safety concern."[3] Therefore, it is not in dispute that original Zosyn® was not discontinued for safety and efficacy reasons.

For this and the other reasons set forth in the above-referenced citizen petition dockets, FDA regulations clearly permit the Agency to accept and approve ANDAs for parenteral drugs that contain different inactive ingredients from the RLD, when, as in the case here, the difference in inactive ingredients does not affect the safety and effectiveness of the proposed generic drug product.[4] While chelating agents (such as EDTA in reformulated Zosyn®) are not among the types of inactive ingredient that FDA's regulations provide may differ between an RLD and generic product, such differences are clearly contemplated by FDA's broad waiver authority under 21 C.F.R. § 314.99(b). Wyeth itself has confirmed that the omission of the inactive ingredients citric acid monohydrate and EDTA does not affect the safety or effectiveness of Zosyn®.

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1 Zosyn® (piperacillin and tazobactam for injection), 40.5 g pharmacy bulk vial is identified in the Prescription Product list of the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) (NDA 50-684). A printout of this listing by active ingredient details is provided in **Annexure – 1**

2 Sandoz Inc. (Sandoz) Citizen Petition, November 1, 2005 (2005P-0456); Rakoczy (Rakoczy) Molino Mazzochi Siwik LLP Citizen Petition, May 9, 2006 (2006P-0195).

3 *See* FDA Docket 2005P-0456/C1 (Wyeth Comments to Sandoz Petition).

4 *See, e.g.,* 21 CFR § 314.94(a)(9)(iii).

The labeling for a proposed drug product would be substantially the same as the labeling for the previously approved formulation of the Reference Listed Drug Zosyn® (piperacillin and tazobactam for injection), Pharmacy Bulk Package. A copy of the previously approved package insert for the reference listed product Zosyn® and the copy of the package insert for a proposed generic drug product is provided in **Annexure – 2** and **Annexure – 3** respectively.

FDA's acceptance of ANDAs for the previously-approved formulation of Zosyn® in 40.5 g pharmacy bulk vial, as well as in the dosage forms identified in the Sandoz and Rakoczy citizen petitions, would be consistent with the legislative intent underlying the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act), which was enacted to "encourage competition by decreasing the time and expense of bringing generic drugs to market, and there by to provide the public with low cost drugs."[5] In contrast, FDA's failure to accept and review ANDAs for the previously-approved formulation of Zosyn® would provide the innovator (Wyeth) – and if Wyeth's arguments are accepted, other innovators – with the means to delay and prevent approval of generic versions of their products, simply by making minor modifications to their drug products (irrespective of whether such modifications are needed to address issues of safety or effectiveness) and obtaining patent protection on the new formulations. Indeed, by engaging in this conduct, an innovator company could indefinitely, if not permanently, prevent generic competition by seeking and obtaining new patents on a serial basis. This result would be scientifically unwarranted and would contravene the principles of public policy and legislative intent embodied in the Hatch-Waxman Act.

Accordingly, the petitioner believes that the information provided in this Citizen Petition supports the fact that the discontinued formulation of the Reference Listed Drug, Zosyn® (piperacillin and tazobactam for injection) 40.5 g pharmacy bulk vial, was not discontinued for safety and efficacy reasons.

[5] 54 Fed. Reg. 28,872, 28,874 (July 10, 1989).

C. Environmental Impact

Any Environmental Impact Analysis Report for the action requested is not required as cited under 21 CFR 25.31 (a).

D. Economic Impact

Information regarding economic impact will be made upon request.

E. 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 is unfavorable to the petitioner.

Respectfully Submitted,

IBasade October 23, 2006

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Annexures:
(1) Copy of the relevant page of Orange Book
(2) Copy of the previously approved package insert for the reference listed product Zosyn®
(3) Copy of the package insert for the proposed generic drug product