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Wyeth

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. FDA-2006-P-0019; Zosyn® (piperacillin/tazobactam)

Dear Sir or Madam:

Wyeth submits this supplement to its citizen petition regarding generic piperacillin/tazobactam products to inform the Agency of recent research suggesting that such generic products may have reduced effectiveness compared to reformulated Zosyn®. Because generic applications do not include data pertaining to this issue, the issue may not be evident to FDA as it considers the ANDA applications seeking to market generic versions of piperacillin/tazobactam and Wyeth's related citizen petition raising other concerns about these products.

In particular, recent studies demonstrate that generic versions of piperacillin/tazobactam marketed outside the United States exhibit diminished *in vitro* potency in standard microbial potency assays as compared to Wyeth's reformulated version of Zosyn®. Additional experiments performed by Wyeth suggest that the loss of efficacy for at least one of these generic products may be related to differences in manufacturing methods that result in the formation of piperacillin-tazobactam "zwitterionic" complexes not observed with Wyeth's Zosyn® formulation. At a minimum, these *in vitro* potency differences raise serious questions of whether the manufacturing processes employed by generic manufacturers of piperacillin/tazobactam are adequate to preserve the identity, strength, quality and purity of their generic drug products, as required by statute and FDA's implementing regulations. *See* 21 U.S.C. § 355(j)(4)(A); 21 C.F.R. § 314.127(a)(1).

Specifically, Jones *et al.*, "In vitro potency evaluations of various piperacillin/tazobactam generic products compared with the contemporary branded (Zosyn®, Wyeth) formulation," *Diagnostic Microbiology and Infectious Disease* 61:76-79 (2008) (Tab 1) report testing, funded in part by a research grant from Wyeth, of 23 generic piperacillin/tazobactam products manufactured by 15 different manufacturers. Several of these generic manufacturers, including Aurobindo and Orchid Healthcare ("Orchid"), are believed to have filed ANDAs

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seeking to market generic piperacillin/tazobactam formulations in the United States. Incremental broth microdilution assays ("MIC assays") in four different strains of bacteria were applied to the generic products and compared to the results obtained with Zosyn®. The generic piperacillin/tazobactam products exhibited an average -16% decrease in potency as compared to Zosyn®.

More recently, Professor Ronald Jones of Tufts University and JMI Labs performed additional work, also funded by Wyeth, on a generic piperacillin/tazobactam product manufactured by Orchid. The *in vitro* potency (as determined by MIC assays) of the generic Orchid product was found to be reduced by as much as -42% as compared to Wyeth's formulation. An internal Wyeth report that includes Dr. Jones's data for Orchid's product is attached as Tab 2.

These results suggest that *in vitro* potency differences exist between generic formulations of piperacillin/tazobactam marketed abroad and Wyeth's branded Zosyn® formulation. This diminished potency has the potential to result in negative clinical outcomes, particularly where highly resistant bacterial strains are present in very sick patients.

To better understand the loss of potency exhibited by Orchid's piperacillin/tazobactam formulation, Wyeth scientists performed several experiments. These included a comparison of the pH titration curves of Wyeth's Zosyn® product with that of Orchid's product and an analysis of the concentration of the piperacillin and tazobactam active ingredients at various points along the pH titration curve of Orchid's product. As further described in Wyeth's internal report in Tab 2, the results of these experiments suggest Orchid's manufacturing process results in the formation of piperacillin/tazobactam "zwitterionic" complexes. The formation of such complexes by the active ingredients may provide an explanation for the observed reduction in *in vitro* potency observed with Orchid's formulation.

Wyeth submits that, before approving any ANDA applications seeking to market generic versions of piperacillin/tazobactam, FDA should inquire further into these observed differences in potency and take steps to fulfill its statutory and regulatory mandate that no generic product be approved unless the manufacturing processes employed are adequate to ensure and preserve the identity, strength, quality and purity of that product as compared to the reference listed drug. *See* 21 U.S.C. § 355(j)(4)(A); 21 C.F.R. § 314.127(a)(1).

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If you have any questions, please do not hesitate to contact the undersigned.

Respectfully submitted,

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