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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 about a new compendial standard governing such products. The U.S. Pharmacopeia ("USP") has adopted a final monograph for piperacillin/tazobactam for injection products that includes a heightened standard for particulate testing to ensure the quality and safety of such products over the wide variety of conditions that occur in clinical use.[1]

As the USP explained when it published the draft monograph, acidic conditions (low pH) and metal ions, such as zinc, increase particulate matter formation in piperacillin/tazobactam for injection products.[2] Furthermore, the risk of particulate formation is unpredictable because commercial diluents vary greatly in metal ion content and pH.[3] To reflect the worst conditions that may occur in clinical use, the new monograph, which becomes official in December of this year, requires that any piperacillin/tazobactam for injection product comply with the USP standard for subvisible particulate matter at the extremes of pH and metal ion content likely to be encountered by the drug product in clinical use.

Wyeth submits that it is critical to protection of the public health that FDA require any generic piperacillin/tazobactam for injection product to demonstrate

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[1] *USP32-NF27 Supplement No:2* at 4275 (official date: December 1, 2009) (Tab 1).

[2] *Pharmacopeial Forum* Vol. 34(4):980 (July-Aug. 2008) ("It has been demonstrated that pH variations and the presence of low levels of transition metals in dry or lyophilized preparations of *Piperacillin and Tazobactam for Injection* increase particulate matter formation").

[3] Desai et al., "Zinc Content of Commercial Diluents Widely Used in Drug Admixtures Prepared for Intravenous Infusion," *Int'l J. of Pharmaceutical Compounding* 11(5):426 (2007) (copy previously submitted to the docket).

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compliance with the new monograph standard. Wyeth also believes that this course of action is required by applicable law. The statute requires generic drugs to preserve the identity, strength, quality and purity of the reference-listed drug; such determinations are made in accordance with the standards set forth in the USP.[4] Indeed, FDA's application approval policy specifically states that "reviewers are not to approve regulatory methods/specifications . . . that differ from those in the USP, unless a recommendation is being or has been sent . . . to change the methods/specifications."[5] FDA authors have also acknowledged the need to ensure compliance with USP particulate standards due to the safety concerns raised by these drug contaminants.[6]

The new USP standard is an important step towards protecting the safety of those patients administered piperacillin/tazobactam for injection, and any formulation of those active ingredients approved for injection in patients must meet that standard, as the current formulation of Zosyn® is specifically designed to do. This is required both by due regard for public health and safety and by the existing legal requirements for ANDA approvals.

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

Respectfully submitted,

Geoffrey M. Levitt /gv

Geoffrey M. Levitt

cc: Eric M. Blumberg, Esq.
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[4] 21 U.S.C. §§ 351(b) and 355(j)(4)(A).

[5] CDER Manual of Policies and Procedures: Drug Application Approval 501(b) Policy, MAPP 7211.1 at 2 (Nov. 1, 1995) (emphasis in the original).

[6] Nath et al., *Pharmacopeial Forum* Vol. 30(6):2272 (Nov.-Dec. 2004).