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Wyeth

March 14, 2007

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5360 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 2006P-0173

Dear Sir or Madam:

Wyeth hereby submits additional information to supplement its Citizen Petition submitted on April 25, 2006 (Docket No. 2006P-0173).

The issues raised in Wyeth's Citizen Petition have also been presented to Health Canada. Enclosed for your information is an opinion letter from Coleman Rotstein, M.D. that Wyeth recently submitted to Health Canada. Dr. Rotstein is a U.S. citizen licensed to practice medicine in New York who is currently serving as a Professor in the Department of Medicine and Director of the Division of Infectious Diseases at McMaster University in Ontario, Canada. Of note, Dr. Rotstein is the Chair of the Infectious Disease Service, Hamilton Health Sciences, and an Elected Fellow of the Infectious Diseases Society of America and the American College of Physicians. Dr. Rotstein served as a consultant to Wyeth Canada on this matter.

Wyeth wanted to share this opinion letter with the Food and Drug Administration to the extent that the views expressed by Dr. Rotstein are relevant to medical practice in the United States and to the issues raised in our pending Citizen Petition.

Respectfully submitted,

Geoffrey M Levitt /GML

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Vice President and Chief Regulatory Counsel

2006P-0173

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December 15, 2006

Ms. Marise Lemieux
Business Unit Director, Vaccines and Infectious Diseases
Wyeth Pharmaceuticals
50 Minthorn Boulevard
Markham, Ontario
L3T 7Y2

Dear Ms. Lemieux,

Re: Piperacillin-tazobactam Generic Formulations

You have advised me that Health Canada is now considering the approval of a generic formulation of piperacillin-tazobactam and have requested my views with respect to such an approval. I would like to express my concerns as a medical practitioner about the approval of a generic formulation of piperacillin-tazobactam that may not meet strict standards for compatibility with antibiotics and all the intravenous supportive fluids that may be administered to patients during times of critical illness.

I am referring to the concept of the incompatibility of piperacillin with the aminoglycosides, gentamicin and amikacin. This issue is particularly pertinent when dealing with febrile neutropenic cancer patients who require combination antibiotic therapy consisting of piperacillin-tazobactam and gentamicin. With the advent of the current piperacillin-tazobactam product that provides compatibility with gentamicin, it is common to combine the two antibiotics together in one IV formulation and administer them. This cuts down the number of IV solutions to be constituted. The gentamicin is given once a day whereas the piperacillin-tazobactam is administered three to four times a day. The use of a combination, which has an additive effect in-vitro is highly desirable in neutropenic patients who lack the natural defense provided by neutrophils. If a new generic formulation of piperacillin-tazobactam is incompatible with gentamicin or amikacin, concerns arise whether the patient will be receiving the most effective therapy in their time of need.

Another situation where combination piperacillin-tazobactam and gentamicin or amikacin may be used is for hospital-acquired and ventilator-associated pneumonia. If a patient is predisposed to hospital-acquired or ventilator associated pneumonia due to *Pseudomonas aeruginosa*, combination therapy with piperacillin-tazobactam and gentamicin or amikacin (providing the organism is susceptible to these agents) is

definitely a consideration. In the past, clinicians have opted for the security of combination therapy in *Pseudomonas aeruginosa* pneumonias. In such pneumonias, the issue is not one of receiving antibiotics with an additive or synergistic effect but rather having sufficiently broad coverage to treat even more resistant organisms. Once again, such pneumonias are life threatening and any chance of incompatibility or inactivation when the drugs are combined together as might be seen with a new formulation of piperacillin-tazobactam, must be prevented at all costs.

The last issue I would like to raise is the compatibility of piperacillin-tazobactam with Ringer's lactate. Ringer's lactate is an intravenous fluid used for resuscitation purposes in hypotensive individuals with volume depletion and septic shock. Antibiotics such as piperacillin-tazobactam are often administered simultaneously. The incompatibility of the former preparation of piperacillin-tazobactam with Ringer's lactate was certainly a detriment for physicians. The new formulation of piperacillin-tazobactam that is compatible with Ringer's lactate is definitely an advance and permits adequate resuscitation to occur at the same time as adequate antimicrobial therapy.

My concerns are levied against new generic formulations of piperacillin-tazobactam that haven't been adequately tested for compatibility with aminoglycosides such as gentamicin and amikacin and the resuscitative fluid Ringer's lactate. I do hope that all necessary precautions will be undertaken to ensure that untested generic piperacillin-tazobactam will not produce incompatibilities as posed in the scenarios above. Adequate testing of generic compounds must be performed as has been done with the new formulation of piperacillin-tazobactam prior to any approval.

Sincerely,

Coleman Rotstein MD

Coleman Rotstein M.D.

CR/zd