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Wyeth

December 12, 2006

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

Re: Docket 2006P-0442

Dear Sir or Madam:

Wyeth Pharmaceuticals ("Wyeth") submits these comments in response to the October 23, 2006 citizen petition filed by Orchid Healthcare, a division of Orchid Chemicals & Pharmaceuticals Ltd. ("Orchid"). The petition requests that the Food and Drug Administration ("FDA") determine that Wyeth discontinued its original formulation of Zosyn® (piperacillin and tazobactam for injection) for reasons unrelated to safety or effectiveness. In addition, the petition requests FDA to accept abbreviated new drug applications for generic piperacillin and tazobactam for injection products that duplicate the discontinued Zosyn® formulation.

In its comments, Orchid contends that:

- (1) FDA should exercise its waiver authority under 21 C.F.R. § 314.99(b) to permit a generic product referencing the reformulated version of Zosyn® ("Reformulated Zosyn®") to omit an inactive ingredient in Reformulated Zosyn®, notwithstanding the regulation requiring its inclusion.
- (2) Wyeth's reformulation of Zosyn® consists of minor modifications unnecessary from a safety or efficacy perspective and therefore amounts to nothing more than a "means to delay and prevent approval of generic versions" of Zosyn®.

Wyeth disputes each of these assertions as more fully set forth below. Wyeth also incorporates by reference (1) the citizen petition filed by Wyeth on April 25, 2006 (docket number 2006P-0173) (the "Wyeth Petition"), which requested that FDA refrain from approving any abbreviated new drug application ("ANDA") referencing Original Zosyn® unless the proposed generic product complies with U.S. Pharmacopeia ("USP") particulate standards and demonstrates the same

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compatibility profile as Reformulated Zosyn®; and (2) the comments filed by Wyeth on January 20, 2006 (docket number 2005P-0456) (the “Wyeth Comments”), which opposed a citizen petition requesting that FDA determine that the discontinued formulation of Zosyn® was not discontinued for reasons of safety or effectiveness.

I. Background

Zosyn® is a combination parenteral antibacterial product used for treating certain infections. In 2000 and 2001, the original formulation of Zosyn® (“Original Zosyn®”) was found to inconsistently comply with USP particulate standards, even though it did comply with the particulate standards in its approved new drug application. Because of clinical evidence indicating that intravenous treatments with lower levels of particulate contamination are associated with a reduction in adverse events,¹ and based on a number of scientific and compliance concerns discussed herein in Section III (A), Wyeth reformulated Original Zosyn® so that the product would meet current USP particulate standards across all admixture conditions commonly encountered in the clinical setting.

The reformulated version of Zosyn® (“Reformulated Zosyn®”) contains a functional chelating agent, edetate disodium dihydrate (“EDTA”), and a buffer, citric acid monohydrate, two ingredients not included in Original Zosyn®. These additional ingredients not only allowed the product to comply with USP particulate standards, but also expanded the product’s compatibility profile. Reformulated Zosyn® has a broader compatibility profile than Original Zosyn® in that it is compatible with additional products: Lactated Ringer’s Solution and two commonly used aminoglycoside antibiotics, amikacin and gentamicin.²

¹ KH Falchuck, et al., *Microparticulate-induced phlebitis. Its prevention by in-line filtration*, 312 *New Eng. J. Med.* 78 (1985); Hans-anton Lehr, et al., *Particulate Matter Contamination of Intravenous Antibiotics Aggravates Loss of Functional Capillary Density in Postischemic Striated Muscle*, 165 *Am. J. Respiratory and Critical Care Med.* 514 (2002); R. Leon Longe, *Particulate Contamination in Selected Parenteral Drugs*, 27 *Can. Anesthesia Soc’y J.* 62 (1980). Attached as Exhibits A, B, and C, respectively.

² Zosyn® is indicated, in combination with an aminoglycoside antibiotic, for the treatment of Hospital Acquired Pneumonia (HAP caused by *pseudomonas aeruginosa* or severe infections).

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II. FDA Should Not Waive the Requirement That a Generic Product Contain the Same Inactive Ingredients as its Reference Listed Drug

A. FDA Regulations Require that Generic Versions of Zosyn® Contain EDTA

Generally, a generic parenteral drug must contain the same inactive ingredients as the reference listed drug (“RLD”), although differences in preservatives, buffers, and antioxidants are permitted.³ Because citric acid monohydrate acts as a buffer in Reformulated Zosyn®, a generic product referencing Reformulated Zosyn® could omit citric acid monohydrate or use a different buffer, provided that the resulting product is equally safe and effective and meets all other requirements applicable to the product, including limitations on particulate matter.

EDTA, on the other hand, acts as a functional chelating agent in Reformulated Zosyn® and therefore cannot be omitted from or substituted for in the same manner as a preservative, buffer, or antioxidant. For this reason, EDTA must be included in generic versions of Reformulated Zosyn®.

B. Orchid’s Citizen Petition is Inadequate to Justify a Waiver of the Requirement That a Generic Zosyn® Product Contain EDTA

Orchid claims that FDA may waive the requirement that a generic parenteral product contain the same inactive ingredients as its RLD when “the difference in inactive ingredients does not affect the safety and effectiveness of the proposed generic drug product.” As support for this claim, Orchid cites 21 C.F.R. § 314.94(a)(9)(iii), which allows approval of a generic product that differs from its RLD in preservative, buffer, or antioxidant, provided that the difference does not affect the safety or efficacy of the proposed drug product. Orchid asserts that because no change in safety or effectiveness is the standard for allowing different preservatives, buffers, and antioxidants, the same standard should apply to allow differences in any other types of inactive ingredients. Had FDA intended such a policy, however, the regulation would not have been limited to preservatives, buffers, and antioxidants. Orchid’s reliance on § 314.94(a)(9)(iii) therefore does not support its request for a waiver.

Orchid’s citizen petition does not address the particulate and compatibility issues that would arise if a generic Zosyn® product did not include EDTA as an ingredient. As discussed in detail in the Wyeth Petition, a generic Zosyn®

³ 21 C.F.R. § 314.94(a)(9)(iii).

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product that does not contain a buffer and EDTA may not comply with USP particulate specifications under all conditions of use or be compatible with Lactated Ringer's Solution, amikacin or gentamicin.

Under 21 C.F.R. § 314.90(a), as incorporated by 21 C.F.R. § 314.99(b), a waiver request must contain either (1) an explanation of why compliance with the requirement is unnecessary or cannot be achieved; (2) a description of an alternative submission that satisfies the purpose of the requirement; or (3) other information justifying a waiver. Orchid's waiver request, however, merely asserts that a difference in inactive ingredients between its product and Reformulated Zosyn® would not affect the safety or efficacy of its product. Significantly, Orchid fails to address either the particulate issue or the compatibility issue that would arise if its product is permitted to omit EDTA. Because Orchid fails to justify why it should be permitted to submit an ANDA for a generic Zosyn® product that does not comply with USP particulate specifications and that exhibits a different compatibility profile than Reformulated Zosyn®, FDA should refuse to grant a waiver of the requirement that a generic Zosyn® product contain EDTA.

C. Public Health Concerns Weigh Against Waiver of the Requirement That a Generic Zosyn® Product Contain EDTA

Although FDA has discretion to waive the requirement that a generic product contain the same inactive ingredients as its RLD, there are two significant reasons why FDA should not waive the requirement in this case. First, doing so is likely to result in the approval of a generic Zosyn® product that is not compatible with the same commonly used concomitant medications or reconstitution diluents as are compatible with Reformulated Zosyn®. A difference in compatibility profiles could give rise to medication errors if health care practitioners make the reasonable assumption that the generic product will behave in the same manner as the branded drug and inappropriately substitute the generic product for Reformulated Zosyn®. As described in the Wyeth Petition, under these circumstances, there is a real potential for confusion and resultant errors in product use that could result in harm to patients.

Second, waiving the requirement of sameness of inactive ingredients in this case would likely result in the approval of a generic product that does not comply with current USP particulate specifications when used with all diluents permitted under its label. This is because the product would be based on Original Zosyn®, and Original Zosyn® was not robust enough to meet current USP particulate specifications under all conditions of actual use. It is therefore unlikely that a

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product based on Original Zosyn®, like the generic products proposed by Orchid, would meet those specifications.

Differing compatibility profiles of branded drugs and their generic counterparts, as well as non-compliance with current USP particulate standards, are therefore significant concerns that weigh against waiver of the requirement that products referencing Reformulated Zosyn® contain the same inactive ingredients as Reformulated Zosyn®

III. Wyeth's Reformulation of Original Zosyn® Arose From Scientific and Compliance Concerns, Required a Significant Commitment on Wyeth's Part, and Resulted in Significant Benefits for the Drug Product

Orchid implies in its citizen petition that Wyeth reformulated Zosyn® to prevent generic competition and that the reformulation consisted of minor modifications that were unnecessary from a safety or efficacy standpoint. Contrary to Orchid's insinuations, Wyeth's decision to reformulate arose from scientific and compliance concerns, required a substantial commitment on Wyeth's part, and resulted in significant benefits for the drug product.

A. Wyeth's Reformulation of Original Zosyn® Arose From Scientific and Compliance Concerns

One factor contributing to Wyeth's decision to reformulate was the discovery of unexpected particulate levels in certain batches of Original Zosyn®, which led to a number of direct communications with FDA regarding particulate matter formation in the product. Another factor was Wyeth's experience with particulate formation in one of its other products, Protonix® IV (pantoprazole sodium) for Injection ("Protonix® IV"). The inability of Original Zosyn® to comply with evolving USP particulate standards also factored into the decision to reformulate. These three factors are discussed in detail in the Wyeth Comments and in the Wyeth Petition, and are summarized below.

In 2000 and 2001, certain batches of Original Zosyn® were found to contain unexpected levels of particulate matter. This discovery led to a series of communications between Wyeth and FDA regarding particulate levels in Original Zosyn®, during the course of which FDA indicated that those levels should be reduced. As a result of these communications, Wyeth immediately began investigating methods by which particulate levels could be controlled. Wyeth also committed to FDA that it would study the nature and cause of particulate formation in Original Zosyn® in order to resolve the issue.

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At the time, Wyeth was also developing Protonix® IV. During the approval process, FDA expressed concern about particulate levels in the product. Consequently, FDA required that an in-line filter be packaged with each vial of Protonix® IV until particulate counts could be reduced to acceptable levels. FDA also required Wyeth to make certain post-marketing commitments, including: (1) identification of conditions that promote precipitation in Protonix® IV, (2) evaluation of the effect of commonly used diluents on particulate formation, and (3) reformulation of the product to reduce particulate levels.

Because Original Zosyn® and Protonix® IV had similar particulate issues, Wyeth expected that FDA would require a reformulation of Original Zosyn® as well. In addition, USP was beginning the process of developing a monograph for piperacillin and tazobactam for injection. The product monograph was expected to incorporate the tightened 1995 USP particulate matter specifications and test method set forth in General Chapter <788>.

B. Wyeth's Reformulation of Original Zosyn® Required a Substantial Commitment on Wyeth's Part

The development of a product monograph that would reflect more stringent USP standards, coupled with prompting from FDA to reduce particulates in Original Zosyn® and Protonix® IV, led Wyeth to commit to FDA that it would both study the cause of particulate formation in Original Zosyn® and reformulate Protonix® IV. These commitments were substantial in that they required extensive testing and analysis of the products under all conditions of use permitted under their labels.

It was only as a result of this commitment that Wyeth came to understand that particulate formation in Original Zosyn® is generally caused by (1) precipitation in solutions with low pH or (2) chemical reactions that are catalyzed by metal ions. Wyeth's research efforts also led to the discovery that pH levels and metal ion concentrations of commercial intravenous fluids vary substantially, not only across manufacturers, but also within lots of the same product produced by the same manufacturer.

C. Wyeth's Reformulation of Original Zosyn® Resulted In Significant Benefits for the Drug Product

Wyeth's increased understanding over time of the mechanisms of particulate formation in Original Zosyn® resulted in a reformulation of the product. This reformulation ensured that the product would, under all conditions of use, comply

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with FDA expectations, as well as with USP particulate matter specifications, and consequently reduce the potential for the infusion of undesirable levels of particulates into patients. In addition, the reformulation resulted in an expanded compatibility profile for Reformulated Zosyn®, including compatibility with Lactated Ringer's Solution and two commonly used aminoglycoside antibiotics, amikacin and gentamicin.

In sum, Wyeth undertook the reformulation of Original Zosyn® in response to external scientific and regulatory developments, including FDA's concerns regarding particulate matter in the product, FDA's mandate to reformulate Protonix® IV, and tightened USP specifications. Reformulation required a substantial commitment from Wyeth in terms of research and development and ultimately resulted in an improved product. Reformulated Zosyn® not only consistently complies with current USP particulate standards under all conditions of use, but also exhibits an expanded compatibility profile.

IV. Conclusion

For the reasons set forth above, Orchid's citizen petition requesting that FDA determine that Wyeth discontinued its original formulation of Zosyn® for reasons unrelated to safety and effectiveness and requesting that FDA accept abbreviated new drug applications for products duplicating the original Zosyn® formulation should be denied.

Respectfully submitted,

Handwritten signature of Geoffrey M. Levitt in cursive, followed by the initials JLL.

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