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Wyeth

July 19, 2006

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

Re: Docket 2005P-0456

Dear Sir or Madam:

On January 20, 2006, Wyeth Pharmaceuticals ("Wyeth") filed comments (the "Wyeth Comments") to the November 1, 2005, citizen petition filed by Sandoz Inc. ("Sandoz"). In that petition, Sandoz requested that the Food and Drug Administration ("FDA") determine that a discontinued formulation of Zosyn® (piperacillin and tazobactam for injection) was not discontinued for reasons of safety or effectiveness (the "Citizen Petition"). On April 27, 2006, Abraxis Pharmaceutical Products ("Abraxis") filed comments supporting the Citizen Petition and opposing the Wyeth Comments (the "Abraxis Comments").

In its comments, Abraxis contends that:

- (1) Compliance with U.S. Pharmacopeia standards for subvisible particulate matter will not pose a problem for a proposed product that references Zosyn® but which does not include edetate disodium dehydrate ("EDTA") or citric acid monohydrate (a "Generic Product").¹
- (2) A Generic Product may substitute and/or eliminate EDTA from its formulation because EDTA is a preservative for purposes of 21 C.F.R. § 314.94(a)(9)(iii).
- (3) The inclusion of EDTA and citric acid monohydrate does not have a therapeutic effect in the reformulated version of Zosyn®.

¹ USP <788> "Particulate Matter for Injections." The USP standards currently require that injectable products have fewer than 6000 particles $\geq 10\mu\text{m}$ and fewer than 600 particles $\geq 25\mu\text{m}$.

2005P-0456

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- (4) Risk management plans advising health care practitioners of the differences in conditions of use between a Generic Product and Zosyn® are unnecessary.

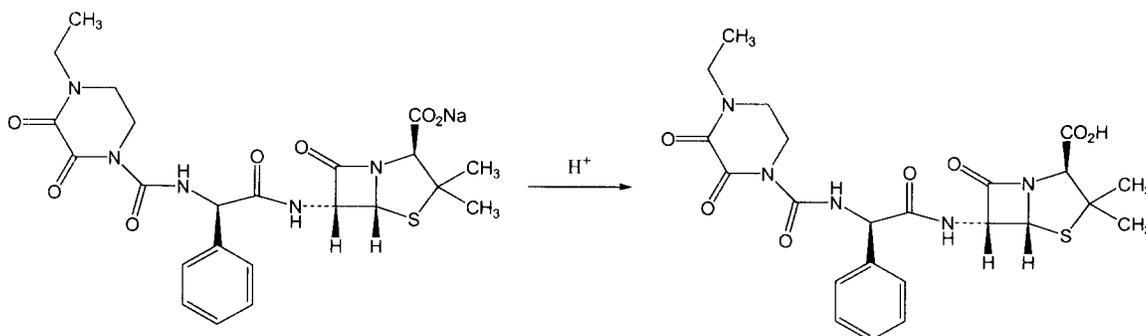
Wyeth disputes each of these assertions as more fully set forth below.

I. The Absence of EDTA and Citric Acid Monohydrate is Likely to Affect a Generic Product's Ability to Comply with U.S. Pharmacopeia ("USP") Standards for Subvisible Particulate Matter

Abraxis suggests that compliance with USP standards for particulate matter in injectable drugs will not pose a problem for Generic Products because it is unlikely that such products will form unacceptable levels of particulate matter. The only support given for this assertion, however, are the claims by Abraxis that formation of insoluble piperacillin monohydrate in aqueous solutions of piperacillin sodium is "highly unlikely" and "very improbable." Abraxis does not cite any scientific evidence explaining why the formation of insoluble piperacillin particles is so unlikely or improbable.

Wyeth has extensively studied the formation of particulate matter in the original formulation of Zosyn® in order to understand the chemical processes by which soluble piperacillin sodium converts into insoluble piperacillin particulates. First, particles were observed to form in solutions prepared with the original formulation of Zosyn® and acidic diluents. Figure 1 describes the chemical process by which such particles form.

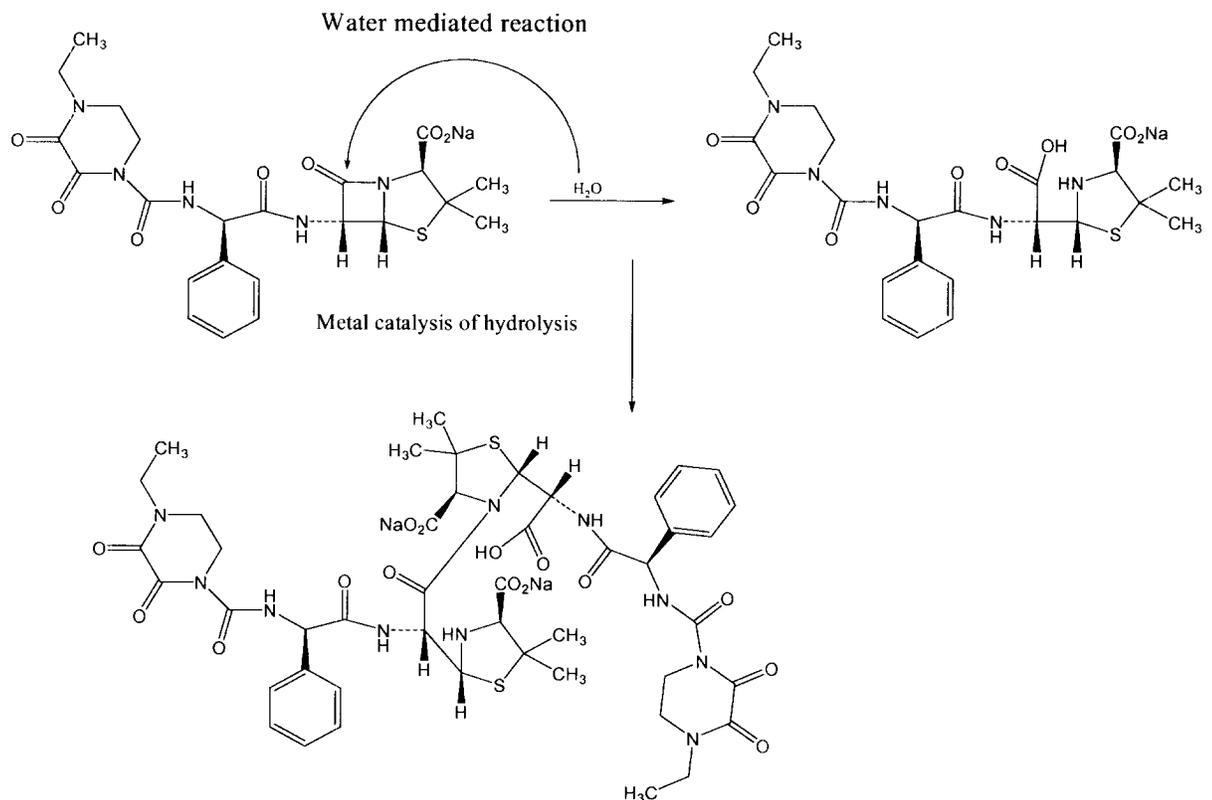
Figure 1
Conversion of Soluble Piperacillin Sodium into an Insoluble Free Acid



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Second, pH shifts in solutions of the original formulation of Zosyn® can also cause the formation of particulate matter. Such shifts can result from both natural aging of the product and from admixture with acidic diluents. When such shifts occur, hydrolysis of the piperacillin compound can open the compound's beta-lactam ring. This, in turn, creates a chemically reactive site with an affinity for amine groups. Because piperacillin itself contains amine groups, dimers of piperacillin, which are insoluble, can form and thereby increase levels of particulate matter (see Figure 2). Furthermore, because the beta-lactam ring is the source of the piperacillin compound's microbiologic activity, hydrolysis of that ring essentially renders Zosyn® inactive.

Figure 2
Hydrolysis of Piperacillin Followed by Formation of Piperacillin Dimer



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Formation of insoluble piperacillin monohydrate and insoluble dimers of piperacillin is accelerated when metal ions are present.² Wyeth also determined during the course of its research that the highest levels of particulate matter occur when the diluent has a low pH and/or a high metal content.

The effect of pH and metal ion content on particulate formation is significant because the pH and metal content of commercial diluents varies greatly. Metal ion concentration and pH levels in commercial intravenous fluids vary not only across manufacturers, but also between lots of the same product produced by the same manufacturer.³

Due to the wide variability in pH and metal ion concentration of commercial diluents, drug products based on the original formulation of Zosyn® would also be susceptible to particulate formation under certain circumstances. Such products must therefore be tested across the spectrum of commercially available diluents permitted under their labels to ensure compliance with USP particulate specifications. If such products are not tested under a range of circumstances (e.g., dilution with acidic diluents with high metal ion concentration), it is uncertain whether those products will meet USP specifications when used in clinical practice.

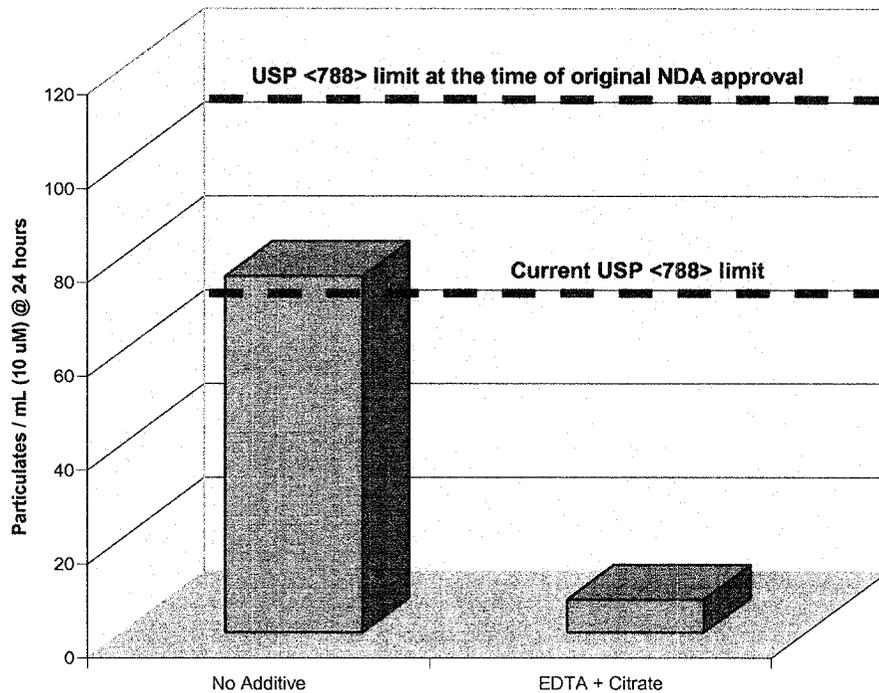
Abraxis also goes so far as to state that “there is no scientific explanation” that would suggest that piperacillin-tazobactam products lacking EDTA and citric acid monohydrate might have unacceptable particulate levels. Wyeth’s experience with the original formulation of Zosyn®, which is a piperacillin-tazobactam product that does not contain EDTA or citric acid monohydrate, provides such a “scientific explanation.” The original formulation of Zosyn®, while robust enough to meet the USP specifications in the approved new drug applications for Zosyn®, is not in fact robust enough to meet the current, tighter USP specifications that were implemented in 1995 (see Figure 3). This fact indicates that piperacillin-tazobactam products lacking EDTA and citric acid monohydrate are unlikely to comply with current USP particulate standards.

² See Kaori Bando, et al., *Metal Induced Degradation of β -lactams*, 39 *Chemotherapy* 315, 318 (1991) (finding that metals affect the degradation profile of beta-lactams like piperacillin by “cleaving” the beta-lactam ring and catalyzing degradation).

³ For a more detailed discussion of the variability of pH and metal concentration in commercially available diluents, see the Citizen Petition filed by Wyeth on April 25, 2006 (docket number 2006P-0173).



Figure 3
Effect of Chelating Agent/Buffer Complex
On Formation of Particulates $\geq 10\mu\text{m}$ in Zosyn® at 24 Hours



II. Substitution for or Elimination of EDTA From a Generic Product is Not Permitted Under 21 C.F.R. § 314.94(a)(9)(iii)

Generally, a generic injectable drug must contain the same inactive ingredients as the reference drug, although differences in preservatives, buffers, and antioxidants are permitted.⁴ Abraxis argues that EDTA is a “preservative” for purposes of 21 CFR § 314.94(a)(9)(iii) because it possesses antimicrobial properties and has been used as a preservative in another injectable product. Regardless of the claims made by Abraxis, however, EDTA in Zosyn® acts as a chelating agent, not as a preservative, and prevents metal ions in solution from reacting with the drug product. Because EDTA in Zosyn® does not function as a preservative, buffer or antioxidant, a Generic Product may only be approved if it includes EDTA.

⁴ 21 C.F.R. § 314.94(a)(9)(iii).

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III. Inclusion of EDTA and Citric Acid Monohydrate Has a Therapeutic Effect in the Reformulated Version of Zosyn®

Abraxis claims that the presence or absence of EDTA and citric acid monohydrate in Zosyn® “has no clinically observed therapeutic effect.” Wyeth disagrees with this claim. The only difference between the original formulation of Zosyn® and the reformulated version is that the reformulated version contains EDTA and citric acid monohydrate. Unlike the original formulation, however, the reformulated version has an expanded compatibility profile that allows the product to be used concurrently with certain aminoglycoside antibiotics and with Lactated Ringer’s Solution. This expanded compatibility arose from the change in formulation and can thus be attributed to the presence of EDTA and/or citric acid monohydrate. Because expanded compatibility with other drug products is, in and of itself, a type of therapeutic effect, the inclusion of EDTA and/or citric acid monohydrate does, in fact, have a clinically therapeutic effect.

IV. Risk Management Plans Advising Healthcare Providers of the Differences Between a Generic Product and Zosyn® are Necessary to Protect the Public Health

A Generic Product may not exhibit the same compatibility profile as the reformulated version of Zosyn® because it does not contain EDTA and/or citric acid monohydrate. This difference in compatibility profiles increases the risk that health care practitioners will improperly substitute a Generic Product for Zosyn® (e.g., when using with Lactated Ringer’s Solution or certain aminoglycoside antibiotics). During the brief period that the original and reformulated versions of Zosyn® were concurrently available on the market, Wyeth conducted an extensive communication program directed at health care practitioners to address this risk (the “Wyeth Program”).

Abraxis suggests the Wyeth Program is sufficient to address the risks presented by a Generic Product that does not exhibit the same compatibility profile as Zosyn®. Abraxis maintains that because Wyeth has “already communicated the differences” between the original and the new formulations of Zosyn®, any further risk management related to the existence of Generic Product with a different compatibility profile is irrelevant. This assessment is incorrect for several reasons. First, the Wyeth Program was conducted during several months in 2005 and 2006, as the original formulation of Zosyn® was being phased out of the market. By the time a Generic Product is approved by FDA and introduced to the market, too much time will have passed to presume that health care practitioners will (1) remember the differences between the original and revised formulations of Zosyn® communicated by the Wyeth Program and (2) associate

Wyeth

the Generic Product with the original formulation of Zosyn® instead of with the reformulated version. Furthermore, health care practitioners who entered the medical profession after the conclusion of the Wyeth Program will be entirely unaware of the differences between Zosyn® and a Generic Product.

Second, the Wyeth Program was designed to address the risks resulting from the short period of time during which the original and reformulated versions of Zosyn were available concurrently. It did not address or attempt to address issues that would arise if both versions were to continue to be available. The existence of a Generic Product that does not exhibit the same compatibility profile of Zosyn®, on the other hand, would create sustained confusion in the marketplace among health care practitioners. This would create additional risks that the Wyeth Program did not address.

Although Wyeth continues to communicate the new compatibility profile of Zosyn® to health care providers who would benefit from this information, it is no longer communicating the differences between the original and new formulations. Once a Generic Product with a different compatibility program than Zosyn® is introduced to the marketplace, however, the risks of improper substitution and improper administration would not only reappear, but would also be magnified. Therefore, the manufacturer of such a Generic Product should be required to implement a risk management program at least as rigorous as the Wyeth Program, and preferably with the additional components outlined in the Wyeth Comments, to ensure that the risks of confusion and improper administration of a Generic Product are appropriately managed.

Respectfully submitted,



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Regulatory and Research