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

Re: Docket 2006P-0195

Dear Sir or Madam:

On November 1, 2005, Sandoz Inc. ("Sandoz") filed a citizen petition (docket number 2005P-0456) requesting 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 "Sandoz Petition"). On January 20, 2006, Wyeth Pharmaceuticals ("Wyeth") filed comments opposing the Sandoz Petition (the "Wyeth Comments").

On April 25, 2006, Wyeth filed a separate citizen petition (docket number 2006P-0173) (the "Wyeth Petition") requesting that FDA refrain from approving any abbreviated new drug application ("ANDA") referencing Zosyn® unless the proposed generic product complies with U.S. Pharmacopeia ("USP") particulate standards and demonstrates the same compatibility profile as the current formulation of Zosyn®.

On May 9, 2006, Rakoczy Mazzochi Siwik LLP ("Rakoczy") submitted a citizen petition (docket number 2006P-0195) opposing the Wyeth Comments and the Wyeth Petition and supporting the Sandoz Petition.

Rakoczy claims that:

- (1) An ANDA applicant may list the current formulation of Zosyn® ("Reformulated Zosyn®") as its reference listed drug ("RLD"), but then seek approval using the original, and now discontinued, formulation of Zosyn® ("Original Zosyn®").

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- (2) Nothing prohibits FDA from waiving the requirement that a generic product referencing Reformulated Zosyn® contain the same inactive ingredients as Reformulated Zosyn®.
- (3) It is unnecessary to ensure that a proposed product referencing Reformulated Zosyn® but based on Original Zosyn® (an “Original Zosyn Generic”) complies with USP standards for subvisible particulate matter in the manner suggested by Wyeth.
- (4) Risk management plans advising health care practitioners of the different compatibility profiles of Original Zosyn Generics and Reformulated Zosyn® are unnecessary because the labeling for Original Zosyn Generics will provide adequate protection against potential harm related to the administration of those products.
- (5) Wyeth’s reformulation of Zosyn® and its opposition to the Sandoz Petition are driven by Wyeth’s intention to delay and prevent generic competition.

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

I. An ANDA May Not Use Reformulated Zosyn® as its RLD and Then Seek Approval Using a Formulation Based on Original Zosyn®

Rakoczy claims that an ANDA applicant may use Reformulated Zosyn® as its RLD, but then seek approval using a formulation based on Original Zosyn®. Rakoczy argues that because FDA has accepted and approved ANDAs for discontinued formulations of Brevibloc® (esmolol) and Sandostatin® (octreotide acetate), ANDAs for Original Zosyn® should also be accepted and approved.

The Brevibloc® and Sandostatin® examples are distinguishable from the case at hand primarily because (1) the reformulations did not significantly alter the performance of those products and (2) the original formulations of those products did not have issues of compliance with USP particulate level specifications. Original Zosyn®, however, has a compatibility profile that differs significantly from that of Reformulated Zosyn®, as described in detail in the Wyeth Petition. This difference in compatibility profiles should preclude FDA from approving any product that references Reformulated Zosyn® but which does not exhibit the same compatibility profile. In addition, although Original Zosyn® met the particulate specifications set forth in its approved new drug application, it may not consistently meet the tighter USP specifications currently in place, particularly

when tested under all possible conditions of use. Original Zosyn Generics should therefore be required to demonstrate compliance with current USP specifications under all possible conditions of use before being approved.

II. FDA Should Not Waive the Requirement That a Generic Product Contain the Same Inactive Ingredients as Its RLD.

In the case of Sandostatin®, FDA specifically granted a waiver allowing Ben Venue Laboratories (“Ben Venue”) to base its generic product on a discontinued formulation of Sandostatin® but use the new formulation of Sandostatin® as its RLD. Only FDA’s reliance on the waiver regulations in 21 C.F.R. § 314.99(b) permitted Ben Venue’s generic product to bypass the requirement in 21 C.F.R. § 314.94(a)(9)(iii) that a generic parenteral product contain the same inactive ingredients as its RLD.

In this case, however, there are two significant reasons why FDA should not waive the requirement set forth in 21 C.F.R. § 314.94(a)(9)(iii). First, doing so would result in the approval of a product with a different compatibility profile than Reformulated Zosyn®. Wyeth is not aware of any other circumstances in which FDA has approved a generic product that is not compatible with the same commonly-used concomitant medications or reconstitution diluents as its name-brand counterpart.

Furthermore, permitting a generic product to enter the market with a compatibility profile different from that of its branded reference drug raises public health concerns. In the instant case, approving an Original Zosyn Generic would increase the risk of medication errors due to confusion between that product and Reformulated Zosyn®. This concern arises not from the safety of the product itself, but from the presence of generic products that health care practitioners may assume will behave identically to their name-brand counterparts, but which in fact differ significantly in their conditions of use. As outlined 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 for sameness of inactive ingredients in this situation 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 the Original Zosyn® formulation, and Original Zosyn® was determined not to be robust enough to meet current USP specifications under all conditions of actual use. It is therefore unlikely that a product based on Original Zosyn®, like an Original Zosyn Generic, would meet those specifications.

Differing compatibility profiles of branded and generic drugs, along with the issue of compliance with current USP particulate standards, are therefore significant concerns. FDA should not waive the requirement that products referencing Reformulated Zosyn® contain the same inactive ingredients as Reformulated Zosyn®.

III. Rigorous Testing of Generic Products is Necessary to Ensure Compliance with Current USP Particulate Standards.

In response to Wyeth's request for rigorous USP particulate testing of Original Zosyn Generics, Rakoczy asserts, without more, that Wyeth has failed to provide "any reason" why existing requirements for ANDA applicants are not sufficient to ensure compliance with applicable USP standards. In fact, Wyeth has set forth sufficient reasons in the Wyeth Comments and in the Wyeth Petition to demonstrate the need for rigorous USP compliance testing of Original Zosyn Generics.

In sum, the great variability in pH and metal ion content of commercially available diluents necessitates such testing in order for Original Zosyn Generics to demonstrate compliance with USP standards across the broad spectrum of diluents permitted in their labeling. Failing to institute such requirements would permit manufacturers of Original Zosyn Generics to test their products only with diluents that do not affect particulate matter formation (e.g., diluents with low metal content). Testing Original Zosyn Generics with the range of diluents available in clinical practice is therefore the only method of ensuring that such products will meet USP specifications under all conditions of use permitted in their labeling. Failure to meet USP criteria under all conditions of use increases the risk of intravenous injection of particulates that are too large or too numerous, which can lead to adverse health effects.¹

IV. Risk Management Plans Advising Healthcare Providers of the Differences Between Original Zosyn Generics and Reformulated Zosyn® are Necessary to Protect the Public Health

As noted above, it is likely that an Original Zosyn Generic will have a different compatibility profile than that of Reformulated Zosyn®. Health care practitioners

¹ Nrapendra Nath et al., *Particulate Contaminants of Intravenous Medication and the Limits set by USP General Chapter <788>*, 30 Pharmacopeial Forum 2272 (2004). For a more detailed discussion of particulate matter in injectable products, *see also* Wyeth Comments at 2-3 and Wyeth Petition at 3.

who are not made aware of this difference in compatibility profiles will be more likely to improperly substitute an Original Zosyn Generic for Reformulated Zosyn® (e.g., when using Zosyn® with Lactated Ringer's Solution or certain aminoglycoside antibiotics). Because improper substitution of an Original Zosyn Generic for Reformulated Zosyn® may result in inactivation or improper dosing of drug products, it is important to minimize the risk of improper substitution.

Rakoczy claims that the proposed labeling of any approved Original Zosyn Generic will provide "adequate protection against any potential risks related to the administration of the drug product." Wyeth disagrees. Health care practitioners are accustomed to using generic products and their brand name counterparts interchangeably. An Original Zosyn Generic, however, will not be interchangeable with Reformulated Zosyn® because it will not have the same compatibility profile. Health care practitioners are unlikely to be aware of this difference unless they are adequately informed of and reminded of such differences through risk management initiatives.

Wyeth recognized the need to manage this risk during the transition period in which both Original Zosyn® and Reformulated Zosyn® were available. It therefore conducted an extensive communication program directed at health care practitioners to distinguish between Original Zosyn® and Reformulated Zosyn® and thereby address the risk of improper administration of Original Zosyn® (the "Wyeth Program"). Rakoczy claims that the Wyeth Program was merely a self-serving promotional tool designed to convince customers to switch from Original Zosyn® to Reformulated Zosyn®. This assertion is entirely false. First, the Wyeth Program was intended to inform customers of the differences between the two products in order to reduce the risk of improper administration of Original Zosyn®. Second, there was no need to convince health care practitioners to "switch" to Reformulated Zosyn® because that product *replaced* Original Zosyn®.

Rakoczy also argues that manufacturers of Original Zosyn Generics should not be required to implement risk management programs because FDA did not require Wyeth to implement such a program. Wyeth's replacement of Original Zosyn® with Reformulated Zosyn® is not, however, analogous to the introduction of an Original Zosyn Generic to the market. In the former situation, the length of time during which the original and reformulated products were concurrently available was limited, so the risks associated with that overlap were also limited. If, however, an Original Zosyn Generic that has a different compatibility profile than Reformulated Zosyn® is introduced to the market on a long-term basis, those risks would not only reappear, but would also be magnified and extended. Therefore, FDA should require manufacturers of such products to implement risk

management programs 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 those products are appropriately managed.

V. Wyeth Reformulated Original Zosyn® as a Result of Unexpected Particulate Levels in the Product, Its Experience with Protonix® IV, and Evolving USP Particulate Standards

Contrary to Rakoczy's contention that the reformulation of Original Zosyn® was driven by anticompetitive motivations, Wyeth in fact decided to reformulate because of several scientific and compliance concerns. One such factor was Wyeth's 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®, in 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.

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 the product 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, at some point, 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>.

The need to develop a product monograph reflecting 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 dual commitments resulted in Wyeth's discovery that particles in solution made from Original Zosyn® were generally caused by (1) precipitation in solutions with low pH or (2) chemical reactions that were catalyzed by metal ions. Wyeth also discovered that pH levels and metal ion concentrations of commercial intravenous fluids varied substantially, not only across manufacturers, but also within lots of the same product produced by the same manufacturer.

Over time, Wyeth's increased understanding 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 with FDA expectations, as well as with USP particulate matter specifications.

In sum, Wyeth took the initiative to reformulate Original Zosyn® in response to external scientific and regulatory developments, including FDA concerns regarding particulate matter in the product, FDA's mandate to reformulate Protonix® IV, and tightened USP specifications. In doing so, Wyeth preemptively addressed the particulate issues raised by FDA during the Protonix® IV experience and also delivered a robust product that consistently complies with current USP particulate standards when administered to patients.

Respectfully submitted,



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