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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-0173; Supplement to Citizen Petition

Dear Sir or Madam:

Wyeth hereby submits additional information to supplement its April 25, 2006 Citizen Petition (Docket No. 2006P-0173). In that petition, Wyeth noted that its product Zosyn® (piperacillin and tazobactam for injection) had been reformulated and that as a result of the reformulation, the product's compatibility profile had expanded to allow for simultaneous administration with Lactated Ringer's Solution ("LRS") and with two aminoglycoside antibiotics, amikacin and gentamicin. Prior to the reformulation, Zosyn® was not compatible with those products. Given this expanded compatibility profile, Wyeth's petition requested the Food and Drug Administration, *inter alia*, to refrain from approving any abbreviated new drug application referencing Zosyn® unless the proposed generic product demonstrates the same compatibility profile as the current formulation of Zosyn® ("Reformulated Zosyn").

Wyeth is now submitting data indicating that health care professionals are, in fact, widely administering LRS, amikacin, and gentamicin simultaneously with Reformulated Zosyn®. These data support Wyeth's contention that introduction of a generic piperacillin and tazobactam for injection product that does not exhibit the same compatibility profile as Reformulated Zosyn® could create confusion among health care professionals, resulting in medication errors and associated public health risks.

2006P-0173

SUP 4

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# I. SURVEY METHODOLOGY

Wyeth commissioned a survey of nurses and pharmacists on various issues related to Reformulated Zosyn. The Internet-based survey was conducted March 6-13, 2007, by P\S\L Research, a survey firm under contract with Wyeth.

## A. OBJECTIVE

The primary purposes of the survey were (1) to gauge the effectiveness of Wyeth's efforts to communicate marketing messages regarding Reformulated Zosyn to pharmacists and nurses and (2) to determine the relevance of such messages to those health care professionals. These objectives required that the survey be limited to individuals who not only spend a considerable portion of their professional time in a hospital setting and recommend or administer injectable antibiotics to a significant number of patients, but who also had received some type of marketing communication regarding Reformulated Zosyn in the recent past.

## B. DESIGN

The majority of the questions in the survey related to the frequency and type of marketing communications received by the participant, the participant's recall of specific marketing messages, and the quality of the marketing communication. These questions are not relevant to the issues raised in Wyeth's Citizen Petition.

In addition to those survey questions, nurses were asked to answer nine further questions concerning the use of Reformulated Zosyn with either amikacin, gentamicin, or LRS. Pharmacists were asked to answer two additional questions regarding whether they expected the number of patients simultaneously receiving Reformulated Zosyn and LRS, or Reformulated Zosyn and amikacin or gentamicin, to increase, decrease, or remain the same over the following six months. Because the questions asked to pharmacists do not directly relate to the issues raised in the Citizen Petition and discussed in this Supplement, the results presented here relate only to the survey of nurses.

## C. PARTICIPANT RECRUITMENT

P\S\L Research initiated the survey by sending an email message to 17,000 nurses in its database. The nurse database is representative of all regions, practitioner types, and hospital types. The email, entitled "Please share your opinion on a reformulated antibiotic," briefly explained the purpose of the 10-minute survey in

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general terms and contained a link to the survey. The email also offered participants a $25 honorarium.

Given the objectives of the survey, 922 (84%) of the 1094 nurses who responded to the email were excluded from participation in the survey because they (a) spent less than 75% of their professional time in a hospital setting (49%), (b) administered injectable antibiotics to fewer than four hospitalized patients per week (13%), or (c) had not received a communication from Wyeth about Reformulated Zosyn in the previous three months (22%). Of the remaining 172 nurses (16%), the first 150 who completed the survey comprised the survey population, as specified by the survey design.

## II. SURVEY RESULTS

The survey results indicate that large numbers of healthcare practitioners are taking advantage of the expanded compatibility characteristics of Reformulated Zosyn.

### A. COMPATIBILITY WITH AMINOGLYCOSIDES

As noted above, Reformulated Zosyn may be administered simultaneously with gentamicin and amikacin.[1] Almost all hospital nurses in the survey characterized this as a "great improvement" (41%) or "some improvement" (54%). Indeed, nurses in the survey reported that nearly half (46%) of patients receiving Reformulated Zosyn and either gentamicin or amikacin received those therapies simultaneously.[2]

### B. COMPATIBILITY WITH LRS

Of the 150 nurses included in the survey, 124 (83%) answered that they had patients within the last three months who had received both Zosyn and LRS, the average being eleven patients per nurse. Survey participants indicated that of these patients, 43% received Zosyn dissolved in LRS, or simultaneously with

[1] Note that the approved labeling for Reformulated Zosyn recommends that patients with nosocomial pneumonia be treated with Reformulated Zosyn plus an aminoglycoside.
[2] The survey question asked was: "Approximately what percent of patients receiving both Zosyn and gentamicin or amikacin during their hospital stay received them simultaneously or sequentially?" The 46% figure for simultaneous administration of Zosyn with gentamicin or amikacin was calculated by averaging all of the responses given to this question. A weighted average, taking into account the number of patients each respondent reported as being treated with both Zosyn and gentamicin or amikacin, yields a 49% rate of simultaneous administration.

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LRS.[3] The remaining 57% received Zosyn via Y-tube with LRS, but the survey did not differentiate between simultaneous Y-tube administration or sequential Y-tube administration.

## III. IMPLICATIONS OF THE SURVEY RESULTS

As outlined above, the survey found that (1) 46% of patients who received both Zosyn and either gentamicin or amikacin received them simultaneously and (2) at least 43% of patients who received both Zosyn and LRS received them simultaneously. Upon receiving the survey results, Wyeth reviewed available antibiotic usage data and analyzed the survey results in light of this usage data to determine the estimated number of patients who will receive Reformulated Zosyn in a manner that is medically permissible with Reformulated Zosyn (e.g., simultaneously with amikacin, gentamicin, or LRS), but not with the previous formulation. The results of Wyeth's analysis are summarized below.

### A. AMR DATA

Wyeth has access to two sources of data regarding antibiotic usage in hospitals. The first is from Arlington Medical Resources Inc. ("AMR"), an international pharmaceutical market research firm that conducts hospital drug use audits and compiles data on drugs administered to hospital patients. AMR's antibiotic usage data is based on actual chart audits and includes patients who received various combinations of products, such as Zosyn plus gentamicin and Zosyn plus amikacin. AMR does not track usage of LRS, however, so AMR data is not available regarding the use of Zosyn in conjunction with LRS.

Based on 2006 AMR data, Zosyn was concomitantly administered with either amikacin or gentamicin on 611,451 patient days. When multiplied by the rate of simultaneous administration indicated by the Wyeth survey (46%), this suggests that there will be more than 280,000 patient days annually during which Zosyn will be simultaneously administered with those products (See Table 1).[4]

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[3] The survey question asked was: "What percent of your LRS patients that received Zosyn received it in the following fashions: (a) Zosyn dissolved in LRS, (b) Zosyn and LRS administered via a Y-tube." The 43% figure for Zosyn dissolved in LRS (i.e., Zosyn administered simultaneously with LRS) was calculated by averaging the responses given to this question. A weighted average, taking into account the number of patients each respondent reported as being treated with both Zosyn and LRS, yields a 45% rate of simultaneous administration.

[4] This assumes that the rate of concomitant use of Zosyn with amikacin or gentamicin in 2007 will be the same as that in 2006.

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**Table 1**
**Simultaneous Administration of Zosyn with Amikacin, Gentamicin or LRS: 2007 Projected Patient Therapy Days Based on AMR Data**

| | 2006: Actual Patient Therapy Days | X | Surveyed Rate of Simultaneous Administration | = | 2007: Projected Patient Therapy Days |
|---|---|---|---|---|---|
| **Zosyn concomitantly administered with amikacin or gentamicin:** | 611,451 | | 46% | | 281,267 |
| **Zosyn concomitantly administered with LRS:** | No AMR Data | | 43% | | No Projection |
| | **Total Projected Patient Therapy Days of Simultaneous Administration** | | | | **281,267** |

## B. SDI DATA

The second source of data is from Surveillance Data, Inc. ("SDI"), which provides healthcare data and market research to pharmaceutical and healthcare-related companies. The SDI data is based on hospital operational files and other sources, including claims data. Unlike AMR data, SDI measures the number of patients concomitantly receiving Zosyn and another therapy, rather than the number of days during which patients concomitantly receive Zosyn and another therapy.

Based on 2006 SDI data, Zosyn was concomitantly administered with either amikacin or gentamicin in 82,655 patients, and with LRS in 104,832 patients. This data suggests that in 2007, more than 83,000 patients[5] will receive Zosyn administered simultaneously with amikacin, gentamicin, or LRS (See Table 2).[6]

[5] SDI tracks the use of Zosyn with amikacin or gentacimin independent of the use of Zosyn with LRS, and therefore there is the potential that a patient who concomitantly received Zosyn plus LRS plus either amikacin or gentacimin could have been included in both rows of Table 2 and thus double-counted for purposes of determining the 83,099 figure. However, given that the use of Zosyn in conjunction with LRS typically occurs in a different treatment context (e.g., treatment of trauma injuries) than the use of Zosyn in conjunction with amikacin or gentamicin (e.g., treatment of pneumonia), the extent of over-inflation due to this potential for double-counting is likely modest.

[6] This assumes that the rate of concomitant use of Zosyn with LRS in 2007 will be the same as that in 2006.

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**Table 2**
**Simultaneous Administration of Zosyn with Amikacin, Gentamicin or LRS: 2007 Projected Patients Based on SDI Data**

| | 2006: Actual Patients | X | Surveyed Rate of Simultaneous Administration | = | 2007: Projected Patients |
|---|---|---|---|---|---|
| Zosyn concomitantly administered with amikacin or gentamicin: | 82,655 | | 46% | | 38,021 |
| Zosyn concomitantly administered with LRS: | 104,832 | | 43% | | 45,078 |
| | | | | | |
| | Total Projected Patients Receiving Simultaneous Administration | | | | 83,099 |

## IV. CONCLUSION

These data confirm that the concerns Wyeth has raised about the risks of introducing a generic piperacillin and tazobactam for injection product to the market that does not exhibit the same compatibility profile as Reformulated Zosyn are not merely theoretical. Based on Wyeth's survey data, 46% of patients who receive Reformulated Zosyn concomitantly with amikacin or gentamicin, and 43% of those who receive Reformulated Zosyn concomitantly with LRS, will receive those therapies simultaneously. As demonstrated by the AMR and SDI data, many thousands of patients will be prescribed one of those therapies concurrently with Reformulated Zosyn. This translates into thousands of patients who will receive those therapies simultaneously because of the expanded compatibility profile of Reformulated Zosyn, and tens to hundreds of thousands of concomitant infusion events.

Thus, a generic product that purports to be interchangeable with Reformulated Zosyn, but which does not exhibit the same compatibility profile, has the potential to cause significant real-world confusion in the hospital setting, potentially resulting in medication errors and increased risks to patient health. This potential for error exists each time a patient is dosed. Furthermore, introduction of such a generic product to the market will pose an increasing risk to public health over time as more health care practitioners become aware of Reformulated Zosyn's expanded compatibility profile and opt to administer it simultaneously with amikacin, gentamicin, and LRS.

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## V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Supplement includes all information and views on which the petition relies, and that it includes representative data and information known to the petition that are unfavorable to the petition.

Respectfully submitted,

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