CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 50-750

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling				
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-750

Trade Name:ZOSYN in Galaxy Containers PL2040 Plastic)

Generic Name:(piperacillin sodium and tazobacam sodium injection)

Sponsor: Lederle Piperacillin, Inc.

Approval Date: February 24, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 50-750

APPROVAL LETTER

NDA 50-750

FEB 24 1998

Lederle Piperacillin, Inc.
Attention: Ms. Diane Mitrione
170 Radnor-Chester Road
Radnor, Pennsylvania 19087

Dear Ms. Mitrione:

Please refer to your new drug application dated February 24, 1997, received February 24, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zosyn (piperacillin sodium and tazobactam sodium injection) in Galaxy Containers (PL 2040 Plastic).

We note that this application is subject to exception provisions of Section 125(d)(2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated June 9 and 27, July 8 and 10, and November 14, 1997; January 14 and 16 (2), and February 10, 17, and 23, 1998. The User Fee goal date for this application is February 24, 1998.

This new drug application provides for a new formulation in a frozen premix equivalent to current reconstituted, freeze-dried product currently approved for Zosyn (sterile piperacillin sodium and tazobactam sodium) Vials and Pharmacy Bulk Package, NDA 50-684. The premixed, ready-to-use, frozen dosage form of Zosyn will utilize Baxter HealthCare Corporation's PL 2040 Galaxy Plastic container system and will be available in three different dosage strengths including 2.25 g/50mL, 3.375 g/50mL, and 4.5 g/100mL. The new drug products will have the same indications as Zosyn in the vial dosage forms currently approved under NDA 50-684.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated February 23, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on February 23, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated

"FINAL PRINTED LABELING" for approved NDA 50-750. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your chemistry, manufacturing, and controls Phase 4 commitment specified in your submission dated January 14, 1998. This commitment is listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of this commitment. The status summary should include the number of patients entered in each study, any required nonclinical studies, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Stephen T. Trostle, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:

Original NDA 50-750
HFD-520/Div. files
HFD-520/TL/MO/MAlbuerne MAll 2/23/98
HFD-520/MO/MMakhene
HFD-520/MO/RAlivisatos
HFD-520/TL/Micro/ASheldon TS 2/24/98
HFD-520/Micro/JKing As for DK 2/24/98
HFD-520/TL/Chem/DKatague DK 2/24/98
HFD-520/Chem/MSloan MSL 2/24/98
HFD-520/TL/Pharm/ROsterberg ROO 2/24/98
HFD-520/Pharm/KSeethaler K.S. 02-23/98 - K.S. 2/23/98
HFD-520/TL/Stat/DLin
HFD-880/TL/Biopharm/FPelsor FPelsor 2/24/98
HFD-880/Biopharm/HSun HS 2/23/98
HFD-160/StMicro/PHughes
HFD-520/LGavrilovich (with labeling)
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-104/THassall (with labeling)
HFD-101/LCarter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling) ST 02/23/98
HFD-520/RHPM/STrostle/stt/ft/02/23/98 \n50750ap.000

Concurrence only:
HFD-520/C/PMS/JBona for JBona 2-24-98

APPROVAL (AP) [with Phase 4 Commitment]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-750

MEDICAL REVIEW(S)

February 23, 1998

Medical Team Leader Review of NDA 50-750

Date of Submission: February 24, 1997

Name of Drug:
Trade name: Zosyn in Galaxy® Containers (PL2040 Plastic)

Generic Name: piperacillin sodium and tazobactam sodium

Applicant: Wyeth-Ayerst Laboratories

Category: Piperacillin: beta-lactam antibiotic
tazobactam: beta-lactamase inhibitor

Dosage Form: Zosyn® in Galaxy® Containers (PL2040 Plastic)
2.25g, 3.375g, 4.5g

Route of Administration: For intravenous use only

Indications:
Treatment of patients with moderate to severe infections caused by piperacillin resistant, piperacillin/tazobactam susceptible, B-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by Escherichia coli or the following members of the Bacteroides fragilis group:

B. fragilis, B. ovatus, B. thetaiotaomicron, or B. vulgatus

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses, and ischemic/diabetic foot infections caused by Staphylococcus aureus.

Postpartum endometritis or pelvic inflammatory disease caused by Escherichia coli

Community - acquired pneumonia (moderate severity only) caused by Haemophilus influenzae

Nosocomial pneumonia (moderate to severe) caused by Staphylococcus aureus

Background
Zosyn 2.25g, 3.375g and 4.5g single-dose vials and Zosyn 2.25, 3.375g, and 4.5g ADD-Vantage vials are dosage forms approved for the above mentioned indications. The proposed new drug product, Zosyn in Galaxy Containers (PL2040 Plastic) is a frozen, premixed product that after thawed will have the equivalent composition as the marketed freeze-dried products.

Evaluation
There were no clinical efficacy data submitted with this new drug application. The only significant difference between the approved product and the new product is a slightly higher level of residual ethyl acetate (2% w/w) in the new formulation. Ethyl acetate is classified as "generally recognized as safe" by the FDA. Because bioavailability is of no concern in this I.V. dosage form, the applicant's request to waiver the requirement of in vivo bioavailability studies was granted by the Division of Pharmaceutical Evaluation III.

The medical review is, therefore, limited to review of the package insert.

Description - Refer to chemist's review.

Clinical Pharmacology - The only change in this section was substituting throughout.

Microbiology - Refer to microbiologist's review.

Indications and Usage
The seventh, eight, and ninth paragraphs were deleted, and the last sentence of the tenth paragraph was deleted at the Division's request. These changes were acceptable to the applicant.

Contraindications - No changes were made.

Warning - No changes were made.

Precautions - General
In the fourth paragraph,

There were no other changes made.

Adverse Reactions -

Overdosage - No changes were made.

Dosage and Administration - No changes were made.

Directions for use of Zosyn in Galaxy containers (PL2040 Plastic) were added.

Storage recommendation and thawing information were added.

Preparation for administration was added.

How Supplied - Information on the Zosyn Galaxy Containers was added.

References 1 and 3 were updated.

Conclusions and Recommendations.

The final draft labeling submitted February 23, 1998, is acceptable.

It is recommended that NDA 50-750 for Zosyn in Galaxy Containers (PL2040 Plastic) be approved.

/S/

Mercedes S. Albuerne, M.D.
Medical Team Leader

cc: Orig NDA
HFD-520
HFD-520/MO/Makhene
HFD-520/Pharm/Osterberg
HFD-520/Micro/King
HFD-520/Chem/Sloan
HFD-520/CSO/Trostles
HFD-520/Biopharm/Sun

Concurrence:
HFD-520/Div.Dir/Chikami

2/24/98

NFD 520/TROSIR

Medical Officer's Review of NDA 50-750

Date Submitted: February 24, 1997
CDER Stamp Date: March 17, 1997
Date Received by Reviewer: March 16, 1997
Date Review Begun: March 17, 1997
Date 1st Draft Completed: March 18, 1997
Date 2nd Draft Completed: July 1, 1997

Applicant: Lederle Piperacillin Inc.
Wyeth-Ayerst Laboratories
170 Radnor-Chester Road
Radnor, PA 19087
(610) 902-3760

Generic Name: Piperacillin sodium and tazobactam sodium injection

Trade Name: Zosyn® in Galaxy® Containers (PL 2040 Plastic)

Chemical Name: Piperacillin sodium: sodium (2S, 5R, 6R)-6-[®-2-(4-ethyl-2.3-dioxo-1-piperazine-carboxamido)-2-phenylacetamidol]-3,3-dimethyl-7-oxo-4- thia-1-azabicyclo- {3.2.0} heptane-2-carboxylate

Tazobactam sodium: sodium (2S, 3S, 5R)-3-methyl-7-oxo-3- (4-Thia-1-azabicyclo (3.2.0) heptane-2-- (1H-1, 2,3-triazol-1-ymethyl)-4-thia-1-azabicyclo- {3.2.0} heptane-2-carboxylate-4, 4-dioxide- (1H-1, 2,3-triazol-1-ymethyl)-4-thia-1-azabicyclo- {3.2.0} heptane-2-carboxylate-4, 4-dioxide

Chemical Structure: Please see chemistry review

Molecular Formula: Piperacillin sodium $C_{23}H_{26}N_5NaO_7S$
Tazobactam sodium: $C_{10}H_{11}N_4NaO_5S$

Molecular Weight: Piperacillin sodium: 539.5
Tazobactam sodium: 322.3

Pharmacologic Category: beta lactam/beta-lactamase inhibitor combination

Dosage Form: Parental, premixed, ready-to-use, frozen

Route of Administration: Intravenous

Strengths: 2.25g/50 mL
3.375g/50 mL
4.5g/100mL

Proposed Indication and Usage: Zosyn® is indicated for the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, beta-lactamase- producing strains of the designated microorganism...

This NDA has been submitted in order to obtain approval to market Zosyn® in Galaxy® containers. The proposed product is a premixed, ready-to-use, frozen dosage form of Zosyn®. Zosyn® (NDA 50-684) is already approved for the same indications.

No changes have been proposed for the Indications and Usage section of the labeling.

Proposed Dosage and Administration: No changes have been proposed for this section of the current labeling.

Related IND's and NDA's: DMF
DMF
NDA 50-684 (Wyeth-Ayerst)
IND

Material Reviewed: NDA 50-750, Volumes 1.1 and 1.12

Regulatory Background: Zosyn® (NDA 50-684) was approved on October 22, 1993 as a broad-spectrum antimicrobial agent. This combination injectable product consists of a semisynthetic antibiotic, piperacillin sodium and the beta-lactamse inhibitor tazobactam. This product is currently in the form of a lyophilized vial form that must be reconstituted with a suitable diluent per the labeling. There are 4 vial dosages of the lyophilized powder approved: 2.25 g, 3.375g, 4.5 g, and a 40.5 g pharmacy vials.

Baxter Healthcare Corporation has developed for Wyeth-Ayerst a frozen premixed injectable formulation for which they are seeking approval and which would substitute the current vial product. This product is formulated in a dextrose diluent and buffered with sodium citrate dihydrate. The proposed doses and volumes of the premixed formulation will be 2.25 g in 50mL, 3.375 g in 50mL and 4.5 g in 100 mL.

On August 9, 1996, the Applicant submitted a supplemental NDA 50-684/S-008 providing for manufacturing changes to the tazobactam drug substance manufacturing process. This was approved in December 1996. The NDA stability batches for the frozen premixed product were manufactured with the current tazobactam manufacturing process material (NDA 50-684/S-007).

In accordance with an agreement between the Applicant and the DAIDP, via Telecon on July 22, 1996, one batch of each concentration of Zosyn® injection in PL Galaxy® plastic containers has been manufactured by Baxter Healthcare to evaluate the drug product manufactured using the tazobactam drug substance prepared by the revised process. Stability studies are being conducted and will be reported in NDA annual reports.

Chemistry/Manufacturing Controls: Please refer to the Chemistry Review.

Medical Officer's Comment: The *MO questioned the concentration of active drug in each preparation. The Applicant compared the 3.375/50 mL vial product to the premixed product and found the Piperacillin concentrations to be 4.6% and 6% respectively. If the 4.5 gm/50 mL vial product was compared to the 3.375 premixed product, the concentrations were 5.7% and 6% respectively. If the 4.5 vial was compared to the 4.5 premixed product, the concentrations would be 3.3% and 4% respectively. The Applicant concluded that these concentrations are within the ranges used in clinical practice.*

The conclusion drawn from the above is that the concentration in the premixed (new) product is higher than that of the current vial product. The Applicant's representative stated on 3/18/97 in a telecon with the reviewing MO, that the amount of drug being delivered is the same. The higher concentration was

necessary in order to account for the somewhat lower stability and shorter half-life of the premixed-frozen product. The short, 6-month shelf life has been selected because of this factor and the potential loss of active drug by the end of that period.

The MO will defer to the chemistry reviewer for comment.

Microbiology: There is no new microbiology information included in this submission.

Human Pharmacokinetics: The PK of the proposed premixed formulation and the current vial formulation are the same. The plasma half lives of piperacillin and tazobactam are 0.7 and 1.2 hours, respectively, after single or multiple doses. The plasma half life is unaffected by dose or duration of infusion. Both components are primarily excreted in the urine as unchanged drug (65% and 80% respectively). Both are about 30% bound to plasma proteins and are widely distributed to body tissues. The usual adult dose is 12 g of Piperacillin with 1.5 g of Tazobactam in four divided doses. Reduced doses are recommended for patients with a Creatinine clearance less than 40 ml/min.

Human Clinical Experience: This product has not been used or approved in any country including the US.

Clinical Studies: This submission consists of one clinical study designed only to assess if there was a difference between the vial and the premixed formulations in the frequency and severity of the subjective complaint of pain on infusion, using the highest and the lowest concentrations of the premixed product. There is no information on efficacy.

For purposes of comparison, in previous clincial trials of the current formulation in 2621 patients, the incidence of local adverse events was: phlebitis, 1.3%, injection site reaction, 0.5%, pain 0.2%, inflammation, 0.2% and edema, 0.1%.

In the US clinical trials only, pain was reported in 1.7%.

ZOSYN: PAIN ON INFUSION STUDY, Study #95-100

Objective: To assess if there was a difference between the vial and the premixed formulations in the frequency and severity of the subjective complaint of pain on infusion using the highest and the lowest concentrations of the premixed product.

Methods: The study site was provided with the 3.375 gm and the 4.5 gm forms of the premixed frozen formulation as well as the vial form at a strength of 4.5 gm., 5% Dextrose Injection and 0.9% Sodium Chloride Injection were also provided. For thawing, the premixed form is removed from the freezer to a refrigerator for 16 hours and then to room temperature for 60 to 75 minutes. The thawed solution must be given within 8 hours of thawing and both solutions were at room temperature before infusion.

Study Design:

This was a randomized, double-blind, third-party unblinded, cross-over design study to compare the subjective complaint of pain on infusion of the Zosyn® vial and premixed products.
40 subjects, (20 male and 20 female), were to complete study intervals 1 and 2 in a cross-over design. The two intervals were to be 1 week apart as per protocol and were conducted at one study site, The subjects were to remain on site for the entire duration of each interval.

Study subjects were normal adult volunteers who met the inclusion and exclusion criteria. Informed consent was obtained prior to study enrollment and had been approved by the local IRB.
After enrollment and prior to study interval 1, at the time of check-in, the subjects were rescreened to ensure that there had been no changes in their condition. All appropriate information was recorded on the CRFs.

There were 2 groups of patients (20 per group):

Group1- 4.5g/50 ml vial product and 3.375g/50 ml premixed product

Group2- 4.5 g/100 ml vial product and 4.5 g/100 ml premixed product

The order in which subjects were assigned to a group was random according to a randomization schedule.

The study started on July 9, 1996 and ended on July 26, 1996.

The subjects were admitted the evening prior to the study, (9 to 10 hours before the dose administration), and underwent a routine physical exam, urine for drug and alcohol screening and a beta-HCG if the subject was female. Eligibility by verifying that the inclusion and exclusion criteria were met was also performed. If not, the patient was exited from the study. The subjects had free access to fluids and a 20 gauge peripheral vein access device was inserted into a hand vein of each subject. Attempts were made to utilize the same arm and approximate area in all subjects. The catheter was flushed with a saline solution after insertion and again prior to dose administration.

On the day of the drug infusion the pharmacist prepared the vial and premixed products and these were placed in an opaque outer covering so that the nurse performing the infusion remained blinded as to the study agent.

The 50 ml solutions were infused over a minute interval via an IMED pump at a rate of ml/hour and the 100 ml solutions at ml/hour.

Discomfort or pain upon infusion was assessed immediately before in infusion (0 minutes) and at 15, 30, 45, and 60 minutes after the infusion began. The subjects were told the following" We expect there will be some discomfort at the site where the intravenous catheter was inserted." And asked "Are you feeling any stinging, pain or any other feeling of discomfort in the arm where the drug is infusing, other than any discomfort felt by having a catheter inserted?" If the subject answered affirmatively, they were asked to describe the discomfort on a scale from 0 - 10 where 0 was no pain and 10 the worst pain.

After the infusion and the pain evaluation, the catheter was removed and the subjects discharged. There was a 1 week washout period between the study intervals and then the same procedures were again followed for the second interval.

Withdrawal from the study occurred after completion of both intervals or if an adverse event occurred that made it necessary to withdraw the subject as determined by the Investigator.

Only 1 subject was withdrawn before the second interval because of a positive drug screen.

Protocol Overview:

The protocol was simply designed and adhered to. Two modifications were made. The original protocol was completed on June 4, 1996 and amended on June 26, to allow for the insertion for the peripheral IV approximately 2.5 hours prior to infusion (from immediately prior) and again on July 3, 1996 to allow for catheter insertion the night before infusion.

Only one other protocol deviation occurred. This was the inadvertent enrollment of a subject whose weight would have excluded him from the study. This subject was allowed to continue by the Investigator.

The inclusion and exclusion criteria were standard in order to ensure for healthy volunteers. Noteworthy was that patients who were taking prescription or over-the-counter analgesics were excluded.

All subjects were evaluable and based on a sample size of 40, the power of detecting a difference of 1 SD at the significance level of 0.05 is 0.90, where SD is the SD of the difference of the level of pain estimates within a subject. This sample size also allowed for differences between the sexes to be estimated. Data were entered into SAS data sets and verified. Fisher's Exact Test was utilized to determine if there were differences in the incidence of pain between the 2 products.

Medical Officer's Comment: The Reviewer agrees with the design and conduct of the clinical study as presented by the Applicant.

Study Results: (as per the Applicant)

40 subjects were enrolled in the study. 20 subjects to Group 1 and 20 to Group 2. All 40 completed the first interval and 39 the second. The Applicant states that there was no significant difference between the groups in the frequency of pain or the amount of pain related to the time of infusion.

Specifically, of the 40 subjects enrolled, 6 (15%) experienced pain at at least one of the timepoints. Of these 6, 3 reported pain (ranked as a level 2) before infusion and did not report any pain during infusion. 3 (7.7%) subjects experienced pain during the infusion of the premixed product, 1 during infusion of the vial product and 1 experienced pain during both infusions. The p value was 0.26 therefore indicating that there was no statistically-significant difference of pain reported between the 2 products.

On the scale of 1 -10, the average pain level was 1.5 for the vial and 3.0 for the premixed products respectively. The p value for pain intensity was 0.13.

Concentration Comparison: As stated above, there were 20 patients in each group.
One subject from Group 2 (4.5 vial/3.375 premixed) experienced pain during infusion of the premixed product (level 5). 5 subjects from Group 2 (4.5 vial/4.5 premixed) reported pain. Three had pain prior to the infusion of any product, 2 while receiving the premixed product, one while receiving the premixed product and 1 while receiving both products.

The differences were not significant with a p value of 0.18.

Time of Reported Pain: There was no difference between the groups in terms of the time they reported the pain.

Gender Differences: Only women reported pain while receiving medication (3).

Adverse Events: There were NO adverse events reported in this trial and no deaths occurred.

Applicant's Conclusion: "Based on the results of this study, the premix ZOSYN® product is clinically acceptable.

Medical Officer's Comments and Conclusions:

The MO reviewed the Applicant's line listings for all patients, the sample CRF, the protocol and amendments, the consent form and the Applicant's statistical tables and concurs with the Applicant's conclusion.

The MO also noted that a total of 5 patients (6 episodes) from Group 1 (4.5/3.375) reported pain, 2 with the vial product and 4 with the premixed as compared to 1 patient from Group 2 (4.5/4.5) who reported pain only with the premixed product (0 with the vial product). The MO agreed with the severity of pain, and frequency of pain reported by the Applicant in this submission.

Labeling Review:

Medical Officer's Recommendation:

The MO recommends approval of this NDA if there is concurrence from the chemistry and biopharmaceutics reviewers. The MO has determined that there are no safety issues and that the Applicant has adequately demonstrated local infusion site tolerability for the premixed Zosyn®.

The MO recommends the addition of a statement pertaining to the time necessary for thawing in the Directions for Use section of the labeling, as addressed in the protocol for study #95-100.

/S/

Regina Alivisatos, MD
Medical Officer/HFD-590

Concurrence only:
HFD-520/DivDir/Chikami 7/2/97
HFD-590/MTL/Leissa 7/1/97

cc: NDA 50-750
HFD-520
HFD-520/CSO/Trostle
HFD-520/MTL/Albuerne
HFD-880/Biopharm/Sun

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

CHEMISTRY REVIEW(S)

HFD 520 / Trach

JAN 16 1998

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: 50-750 CHEM.REVIEW #: 1 REVIEW DATE: 1/16/98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	2-24-97	2-24-97	2-28-97
AMENDMENT(BC)	6-09-97	6-11-97	6-12-97
AMENDMENT(BC)	6-27-97	6-30-97	6-30-97
AMENDMENT(BI)	7-08-97	7-09-97	7-11-97
AMENDMENT(BL)	7-10-97	7-11-97	7-15-97
AMENDMENT(BC)	11-14-97	11-17-97	11-20-97
AMENDMENT(BC)	1-14-98	1-14-98	1-14-98

NAME & ADDRESS OF APPLICANT:

Wyeth-Ayerst Laboratories
P. O. Box 8299
Philadelphia, PA 19101-8299
(601) 902-3710

CONTACT:

Karel F. Bernady, Ph. D.
Director, Marketed Products
(610) 902-3760

DRUG PRODUCT NAME

Proprietary:	Zosyn®
Established:	Piperacillin sodium and tazobactam sodium
Laboratory Code Name:	CL 227,880 (piperacillin monohydrate) CL 298,741 (tazobactam)
Chemical type	3 S

PHARMACOLOGICAL CATEGORY/INDICATION: Antibiotic; β-lactam

DOSAGE FORM: parenteral
STRENGTHS: 2g/0.25g; 3g/0.375g and 4g/0.5g
ROUTE OF ADMINISTRATION: Injectable
DISPENSED: (X) R_x ( ) OTC

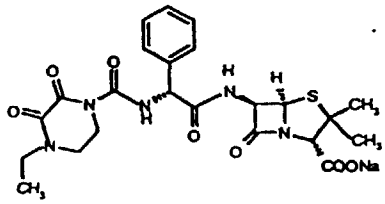
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Piperacillin Sodium, $C_{23}H_{26}N_5NaO_7S$; 539.6 (sodium salt) 535.6 (monohydrate)

Sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-

phenylacetamido]-3,-3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

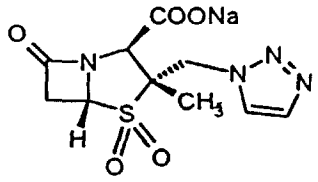
CAS # 59703-84-3 (sodium salt)
61477-96-1 (anhyd. free acid)
66258-76-2 (monohydrate)



Tazobactam Sodium, $C_{10}H_{11}N_4NaO_5S$; 322.3 (sodium salt) 300.3 (free acid)

Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-aza bicyclo[3.2.0]heptane-2-carboxylate, 4,4 dioxide

CAS # 89785-84-2 (sodium salt)
89786-04-9 (free acid)



SUPPORTING DOCUMENTS:

NDA 50-684; DMF DMF

RELATED DOCUMENTS: N/A

CONSULTS:

1) The establishment inspections have an overall acceptable recommendation (Appendix A). Baxter Healthcare Corporation (#1416980), finished dosage manufacturer, packager and labeler was recommended acceptable on Oct. 23, 1997 by Office of Compliance. The other establishments include drug substance manufacturer and , drug substance manufacturer.

2) Environmental Assessment review was prepared and consulted to Nancy Sager, Environmental Scientist, CDER. Responses to deficiencies have been satisfactorily addressed by the applicant. A finding of no significant impact to the environment was concluded and a FONSI statement has been signed (Appendix B).

3) A tradename consult was submitted to Labeling and Nomenclature Committee (Appendix C). Tradename consult indicated no concerns.

4) The applicant requests a waiver of Methods Validation as provided for under 21 CFR § 314.90.

5) A microbiology sterility consult of the CMC indicated some concerns that have been satisfactorily addressed by the applicant (Appendix D).

REMARKS/COMMENTS:

Many of CMC details regarding the drug substance/product were referenced to the supporting NDA 50-684 and were not repeated in this submission. Information about the drug substance in this review was taken from both NDA 50-684 and NDA 50-750.

CONCLUSIONS & RECOMMENDATIONS: *Approvable*

Recommend approval with regard to chemistry, manufacturing and controls. Pending items are a response to justify discontinuation of tests for the impurity of the ring opened piperacillin degradation product (see Phase IV commitment).

/S/ 1-16-98

M. J. Sloan, Ph. D. Review Chemist

cc: Org. NDA 50-750
HFD-520/Division File
HFD-520/CSO/S. Trostle
HFD-520/ChemTL/D. Katague DBJC 1-16-98
HFD-520/Chem/M. Sloan
HFD-520/Pharm/K. Seethaler
HFD-520/Micro/J. King
HFD-590/MO/M. Albuerne
HFD-520/Biostat/D. Lin
HFD-520/Biopharm/H. Sun
HFD-830/Chem/C-w. Chen

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Zosyn®

(Piperacillin sodium and tazobactam sodium injection)

In PL 2040 Galaxy®Plastic Containers

NDA 50-750

FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-750

Zosyn®

Piperacillin sodium and tazobactam sodium injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Zosyn®(piperacillin sodium and tazobactam sodium injection), Lederle Piperacillin, Incorporated(LPI) has prepared an environmental assessment in accordance with *21 CFR 25.31a(a)* (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Zosyn® in PL 2040 Galaxy® Plastic Containers is a sterile semisynthetic combination of piperacillin sodium and tazobactam sodium. It is indicated for the treatment of moderate to severe infection caused by beta-lactamase producing strains of microorganisms that are resistant to piperacillin but are susceptible to the combination of piperacillin and tazobactam. The manufacture of Zosyn® in PL 2040 Galaxy® Plastic Containers will take place at Baxter Healthcare Corporation's manufacturing facility located in Round Lake, Illinois. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

The addition of this process to Baxter's Round Lake facility will not cause the facility to exceed permit limits for wastes, water or air. The manufacture of the drug product will not create any adverse environmental effects. No endangered or threatened species will be affected and natural resources in critically short supply will not be depleted. The applicant used the Tier 0 classification that limits the information submitted in format items 7, 8, 9, 10, 11, and 15, in accordance with the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (Nov. 1995). Under the Teir 0 requirements, both drug substances qualify because their separate and/or combined maximum expected environmental concentration (MEEC) is less than one part per billion (ppb).

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

/S/

7-1-97
DATE

PREPARED BY
Milton J. Sloan, Ph. D.
Chemist
HFD-520

/S/

7-1-97
DATE

DIVISION CONCURRENCE
David B. Katague, PH. D.
Team Leader
HFD-520

/S/

7/5/97
DATE

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachments: Copy of Response Letter from applicant
Copy of EA Deficiences faxed to applicant
Revised Environmental Assessment submitted by applicant
Non-Confidential EA version submitted by applicant

CC: HFD-520/Division File
HFD-357/EA File NDA #50-746
HFD-357/Docket File
HFD-205/FOI COPY

For complete EA review, see Chem Rev. # 1

ENVIRONMENTAL ASSESSMENT

REVIEW

FOR

Zosyn®

(Piperacillin sodium and tazobactam sodium injection)

In PL 2040 Galaxy®Plastic Containers

NDA 50-750

FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

1. Date

21 May 1997

2. Name of Applicant

Lederle Piperacillin, Incorporated (LPI)

3. Address

P. O. Box 8299
Philadelphia, Pennsylvania 19101-1245

4. Description of the Proposed Action

a. Requested Approval

Lederle Piperacillin, Incorporated (LPI) is requesting approval for the manufacture, marketing and use of Zosyn® (piperacillin sodium and tazobactam sodium injection) in PL 2040 Galaxy® Plastic Containers, 2.25 g/50 mL, 3.375 g/50 mL and 4.5 g/100 mL strengths.

This Environmental Assessment, arranged as specified in 21 CFR 25.31a and the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (Nov. 1995), is part of the New Drug Application (NDA) for Zosyn® in PL 2040 Galaxy® Plastic Containers. Zosyn® in PL 2040 Galaxy® Plastic Containers is indicated for the treatment of moderate to severe infection caused by beta-lactamase producing strains of microorganisms that are resistant to piperacillin but are susceptible to the combination of piperacillin and tazobactam.

Zosyn® in vial dosage forms, 2.25 g, 3.375 g, 4.5 g and 40.5 g strengths has been previously approved under NDA 50-684 and has been manufactured and marketed by Wyeth-Ayerst Laboratories. Zosyns® in the vial dosage forms is reconstituted and diluted in 5% dextrose injection or 0.9% NaCl injection prior to patient infusion. To date, no adverse environmental impacts have been observed or reported from the manufacture and use of these products.

The proposed new drug product is a premixed, ready-to-use form of Zosyn® injectable by incorporating Baxter Healthcare Corporation's PL 2040 Galaxy® Plastic container system. Zosyn® in PL 2040 Galaxy® Plastic Containers will be available in three different dosage strengths including 2.25 g/50 mL, 3.375 g/50 mL and 4.5 g/100 mL. Under the proposed action, the drug new products will have the same indications as Zosyn® in the vial dosage forms. The new drug products will not be administered at higher dosage levels, for longer duration than the drug product previously in effect.

Baxter's Galaxy® PL 2040 container system is an established container system which has been approved for several frozen pre-mixed injection products including Nallpen (nafcillin sodium injection) under NDA 50-655 by Baxter. Reference to NDA 50-655 is included to cite previous approval for the PL 2040 container system, and is not intended to provide specific reference to NDA sections for incorporation into this request.

b. Need for Action

The proposed new drug product is indicated for the treatment of moderate to severe infection. Specific indications include appendicitis complicated by abscesses or rupture and peritonitis caused by *Escherichia coli* or Bacteroides fragilis microorganisms; uncomplicated and complicated infections of the skin and skin structure caused by *Staphylococcus aureus*; postpartum endometriitis or pelvic inflammatory disease caused by *Escherichia coli*; moderately severe cases of community-acquired pneumonia caused by Haemophilus influenzae; and nonsocomial pneumonia (moderate to severe) caused by piperacillin-resistant beta-lactamase producing strains of *Staphylococcus aureus*.

c. Production Locations

Drug Substance
Piperacillin monohydrate bulk drug substance will continue to be synthesized according to the approved manufacturing and control information previously submitted to the Zosyn NDA No. 50-684. The manufacturing site for bulk piperacillin will be:

Tazobactam bulk drug substance will continue to be synthesized according to the approved manufacturing and control information previously submitted to the Zosyn NDA No. 50-684. The manufacturing site for bulk tazobactam will be:

Drug Product
Zosyn® in PL 2040 Galaxy® Plastic Containers, the proposed new drug product, will be manufactured and packaged at Baxter Healthcare Corporation, Round Lake, Illinois Facility.

Baxter Healthcare Corporation
Route 120 and Wilson Road
Round Lake, IL 60073

The facility is located in a 515 acre light industrial and research and development campus, wholly owned by Baxter, in rural western Lake County, Illinois. The approximate center of the developed portion of the property is at latitude 42°20'09" North and longitude 88°08'02" West which is at an elevation of 801.8 feet above mean sea level. The terrain is flat to gently rolling with annual average precipitation of 33 inches per year and average ambient temperature of 64.4° F (summer 6 months) and 34.1°F (winter 6 months). Drainage is mainly underground and through intermittent flow to drainage ditches. The property is bordered by state, county and township roads. There are no private dwelling units or commercial establishments on facility property.

Lake County, Illinois is a Non-attainment area with regard to Clean Air Act National Ambient Air Quality Standards. However the facility is in compliance with all parameters contained in its air emission permits.

d. Locations of Use

As a prescribed drug product, Zosyn® in PL 2040 Galaxy® Plastic Containers will be distributed and used worldwide. In the United States locations of use include hospitals, clinics and private practices.

All used containers which contain residues of the drug product will be secured and disposed of in accordance with established procedures at the locations where the new drug product is to be used.

e. Disposal Sites

Returned, recalled, or expired goods will be disposed of in an appropriate manner according to established procedures by Baxter. The points of disposal are located in urban and rural environments throughout the United States.

ACCEPTABLE

5. Identification of Chemical Substances that are Subject to the Proposed Action

For purposes of this Environmental Assessment, the active ingredients of the new drug product, tazobactam and piperacillin, are considered to be the chemical substances that are subject to the proposed action. All other components of the new drug products are commonly used substances and therefore will not be discussed in this environmental assessment.

5.1 a. **Nomenclature** (Tazobactam Sodium)

i. **Established Name (U.S. Adopted Name-USAN)**

Tazobactam Sodium

ii. **Brand/Proprietary Name**

Tazobactam Sodium

(1) **Chemical Abstracts Index (CA) Index Name (inverted form)**

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-methyl-7-oxo-3- (1*H*-1,2,3-triazol-1-ylmethyl)-, 4,4 dioxide, sodium salt, [2*S*-(2α,3β,5α)-,

(2) **Systematic Chemical Name (uninverted form)**

Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1 -ylmethyl)-4-thia-1 azabicyclo[3.2.0]heptane-2-carboxylate, 4,4 dioxide

b. **Chemical Abstracts Service (CAS) Registration Number**

89786-04-9 (free acid)
89785-84-2 (sodium salt)

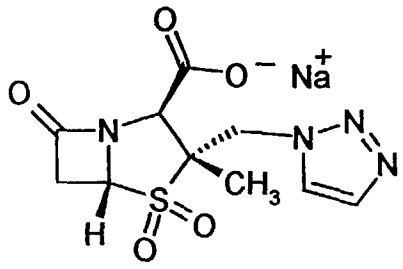
c. **Molecular Formula**

$C_{10}H_{11}N_4NaO_5S$

d. **Molecular Weight**

300.3 (free acid)
322.3 (sodium salt)

e. Structural Formula (Tazobactam Sodium)



5.2 **a. Nomenclature** (Piperacillin Sodium)

i. Established Name (U.S. Adopted Name-USAN)

Piperacillin Sodium

ii. Brand/Proprietary Name

Pipracil™

(1) Chemical Abstracts Index (CA) Index Name (inverted form)

4-Thia-l-azabicyclo[3.2.0]heptane-2carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl) carbonyl]amino] phenylacetyl]amino]-3,3-dimethyl-7-oxo-,monosodium salt, [2*S*-[2α,5α,6β(*S**)]]

(2) Systematic Chemical Name (uninverted form)

Sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2- phenylacetamido]-3,-3-dimethyl-7-oxo-4-thia-l-azabicyclo[3.2.0]heptane-2-carboxylate

b. Chemical Abstracts Service (CAS) Registration Number

61477-96-1 (free acid)
59703-84-3 (sodium salt)

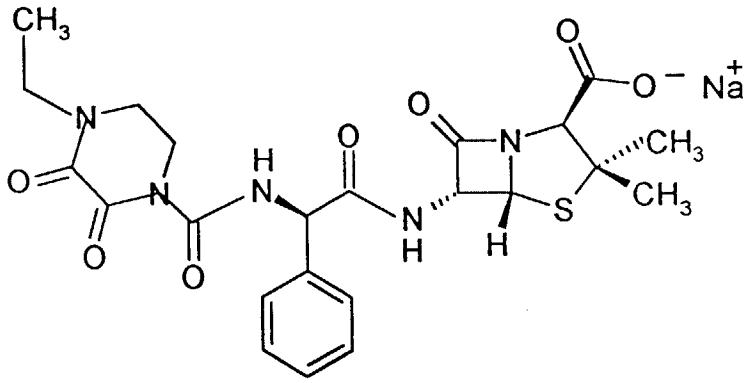
c. Molecular Formula

$C_{23}H_{26}N_5NaO_7S$

d. Molecular Weight

535.6 (monohydrate)
539.6 (sodium salt)

e. Structural Formula (Piperacillin Sodium)



The sodium salt is formed in situ during the preparation of the product formulation. Information concerning physical description, physical/chemical characteristics, additives and impurities of bulk tazobactam and piperacillin is included in Format Item 3 of this NDA file.

ACCEPTABLE

6. Introduction of Substances into the Environment

Introduction of the new drug substances and new products into the environment may take place from (1) the drug product manufacturing facility, (2) the sites that the new drug products are to be used and (3) the sites of the new drug products disposal.

Introduction of the drug substances at the sites of use and disposal are indicated in paragraphs **4d** and **4e** of this document, respectively. Procedures for proper material handling will be followed at these sites in accordance with applicable federal, state and local rules and regulations.

All statements made in this section regarding environmental controls, waste management, employee protection, manufacturing processes, training and emergency procedures refer to the manufacture of the new drug products at Baxter's Round Lake facility.

a. Substances Expected to be Emitted

The new drug products contain tazobactam and piperacillin as active ingredients and the inactive ingredients of the new drug product include sodium citrate and dextrose. The inactive ingredients are commonly used and therefore will not be regarded as substances which are subject to the proposed actions.
The composition of the new drug products is included in Confidential Appendix C.

b. Controls Exercised

Baxter's manufacturing facility, identified specifically in the paragraph 4c, the new drug product manufacturer, is located in Round Lake, Illinois. The drug product manufacturing process is a batch operation in the following sequence: (1) Mixing/Formulation, (2) Filling and (3) Packaging. The Round Lake facility is operating under a number of emission and waste permits which are provided in Appendix A. Manufacturing controls exercised in the Round Lake facility are described below.

Aqueous Waste
The drug manufacturing facility has an on-site wastewater pre-treatment system. Wastewater generated during the manufacturing process will be collected and pre-treated before being discharged to the facility's wastewater system. Pre-treated manufacturing wastewater is further treated in the on-site wastewater treatment plant. The effluent of the treatment plant is discharged into an unnamed drainage ditch tributary to the Squaw Creek under NPDES Permit No. IL0024074.

All process related aqueous wastes containing the drug substances such as unused portion of pre-mixed solution from production batches, equipment and floor cleaning water will also be treated in the pre-treatment system and then the on-site wastewater treatment plant. Aqueous wastes are routinely tested for inhibitory effects to the on-site wastewater treatment plant. To ensure minimal impact to the wastewater treatment process, the aqueous wastes will be subject to physical and chemical treatment when the concentrations of drug substances exceed the inhibitory concentrations. Deactivation of the drug substances contained in process aqueous wastes will be

carried out using sodium hydroxide or by other means.

The proposed action will not cause the treatment plant to exceed its current capacity. Addition of manufacture of the drug product at the Round Lake facility is not expected to cause an exceedance of any NPDES permit limitation.

Air Emission

Emission controls exercised for the manufacture of the new drug products are in compliance with applicable regulations as established by the state and federal EPA. Addition of the drug production in the facility is not expected to cause the facilitv to exceed its permitted limits for air emission.

Dust generated during the manufacture of the new drug products is removed via dust collection systems. The aseptic complex area of the manufacturing facility is equipped with a high efficiency particle air filtration (HEPA) system for removal of particulate matter prior to discharge to the atmosphere. Periodic inspections are conducted by the local authorities to ensure all control devices are operated in accordance with the permit parameters.

Solid/Hazardous Wastes

Solid wastes generated during the manufaeture and paekaging of the drug product may consist ofthe following:

packaging waste
container scrap
product rejects and damaged products
QA/QC samples and related wastes
exhausted HEPA filters used to purify room air and exhaust

Hazardous wastes will be incinerated at an approved off-site facilities in accordance with the Resources Conservation and Recovery Act (RCRA) under a EPA hazardous waste permit ILD067989723. Other domestic solid wastes will be collected and disposed of at approved and licensed landfills in accordance with applicable federal and local regulations.

PL 2040 plastic containers routinely are disposed at local landfill facilities. Under some certain circumstances, a small percentage of the plastic containers may be incinerated at permitted incineration facilities to comply with local requirements.

Pollution Prevention

The facility has in place a pollution prevention program. The participants are actively involved in optimizing production processes, minimizing waste generation and improving waste management

practices for new products such as Zosyn® in PL 2040 Galaxy® Plastic Containers.

Employee Protection

The facility is required to develop a comprehensive environmental plan. As a part of the plan, the facility has developed spill containment procedures based on the chemicals that are handled in the facility. The spill containment procedures include chemical spill cleanup, mitigation and prevention. The procedures take into account total quantities and diversity of chemicals including federal requirements for above ground storage of fuel oils.

Personnel in the drug product manufacturing facility are provided with appropriate personal protective equipment which may include safety glasses, safety shoes, protective gloves and clothing. The manufacturing facility and equipment are designed to minimize employee exposure to hazardous conditions through enpineering, work practice and administrative controls. Employees are trained in the proper operation of equipment to minimize potential safety, health and environmental risks. Extensive safety training is mandated in the facility and Material Safety Data Sheets (MSDS) are available on-site for all chemicals handled in the facility.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

The pollution control devices and waste disposal methods described in paragraph **6b** serve to minimize environmental emissions from the production of Zosyn® in PL 2040 Galaxy® Plastic Containers. The facility complies with the following federal and local regulations.

Clean Air Act, as Amended

Baxter's Round Lake facility is in compliance with federal Clean Air Act, as amended. Currently there are no sources of air emissions that are subject to air permits in the new drug production areas. Addition of this process is not reasonably expected to affect the compliance status of this facility.

Federal Water Pollution Control Act of 1972, the Clean Water Act, and the Water Quality Act of 1987, as amended

The Round Lake facility is in compliance with National Pollutant Discharge Elimination System (NPDES) Permit, NPDES Permit No. IL0024074 as described in paragraph **6b**. Addition of this process is not reasonably expected to affect the compliance status of this facility.

Resource Conservation and Recovery Act (RCRA) of 1976 and Amendments of 1984
Solid Wastes

The facility is in compliance with all federal and local regulations governing hazardous waste generators. Nonhazardous solid waste generated from manufacturing and packaging of the new

drug products will be disposed of at fully permitted landfills. All rejected solid wastes are disposed of at permitted landfill facilities or destroyed at permitted incineration facilities. Any hazardous waste generated in the facility will be destroyed at a RCRA-permitted disposal facility in accordance with all applicable regulations.

Workplace

Potential environmental emissions of the drug substances in the workplace are associated with dusts from active and additive materials and equipment cleaning. Personal safety equipment is worn by operators when handling chemical substances. Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and OSHA standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

Appropriate personal protective equipment is provided to affected employees and its proper use is required. Normal operator attire includes company supplied uniforms, safety glasses or safety hoods, safety shoes, splash goggles, and aprons. Wherever necessary, special safety procedures are enforced to ensure the compliance of all GMP and OSHA standards.

Compliance Statement

Baxter states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Zosyn® in PL 2040 Galaxy® Plastic Containers at its facility in Round Lake, Illinois as well as emission requirements set forth in applicable federal, state, and/or local statutes and regulations applicable to the production of Zosyn® in PL 2040 Galaxy®Plastic Containers at its facility in Round Lake, Illinois. There will be no disruption to the physical environment due to the production of Zosyne in PL 2040 Galaxye Plastic Containers.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The manufacture of Zosyn® in PL 2040 Galaxy® Plastic Containers at Baxter's manufacturing facility located in Round Lake, Illinois will not create any adverse environmental effects. The addition of this process to the facility will not cause the facility to exceed permit limits for wastes, wastewater or air. No endangered or threatened species will be affected and natural resources in critically short supply will not be depleted.

e. Expected Introduction Concentrations

Concentration of Zosyn® in the Environment from Use and Disposal
Zosyn® in PL 2040 Galaxy® Plastic Containers will be distributed to locations throughout the United States. The amount that is eliminated or excreted will enter the wastewater stream. For purposes of this Environmental Assessment, the active ingredients of the new drug product, tazobactam and piperacillin, are used to evaluate environmental release mechanisms and estimate environmental concentrations.

Expected Introduction Concentration (EIC) from Use
The EICs for the aquatic compartment, assuming all tazobactam and piperacillin are used and evenly distributed throughout the United States per day and without metabolism or depletion mechanisms taken into account are stated below. Calculations of the EICs are found in Confidential Appendix E.

EIC for piperacillin = 0.171 x 10-3 mg/L

EIC for tazobactam = 0.021 x 10-3 mg/L

EIC for combined = 0.192 x 10-3 mglL

The EICs for the terrestrial compartment are expected to negligible because any small fraction of the drug substances that might be adsorbed onto the sludge of the wastewater treatment plant will be subjected to further degradation. Sludge from wastewater treatment plants normally is disposed of to sanitary landfill.

The EICs for the atmospheric compartment are estimated to be zero since the drug substances have very low vapor pressures.

Expected Introduction Concentration (EIC) from Disposal
The EICs from disposal are estimated to be insignificant since all rejected batches, damaged product and pharmaceutical waste containing the drug substances are subject to chemical, physical and biological treatment before entering the environment. The amount of the intact drug substances expected to be disposed of in the wastewater treatment plant of the facility will be negligible.

ACCEPTABLE

7. Fate of Emitted Substances in the Environment

a. Tiered Approach to Determining Environmental Fate (EA format item 7) and Effects (EA format item 8)

Expected Environmental Concentrations

The expected environmental concentration (EEC) of tazobactam and piperacillin have been calculated to be 0.002×10^{-3} mg/L and 0.017×10^{-3} mg/L, respectively. These concentrations were calculated by taking the EICs (0.021×10^{-3} mg/L and 0.171×10^{-3} mg/L), a worst case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The results, 0.002×10^{-3} mg/L and 0.017×10^{-3} mg/L, are a conservative estimate of the concentrations of the drug substances in the surface waters of the United States. No further depletion mechanisms have been taken into account in this calculation.

The maximum expected emitted concentration is equal to the expected environmental concentration (EEC) or the expected introduction concentration (EIC), whichever is greater. In the case of tazobactam and piperacillin, the MEEC are 0.021×10^{-3} mg/L and 0.171×10^{-3} mg/L, respectively, the same as the EICs.

Tier 0 Requirements

According to the CDER's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, (Nov. 1995), a drug product will qualify for a Tier 0 classification if its maximum expected environmental concentration (MEEC) is less than one part per billion (ppb).

The MEECs for tazobactam and piperacillin, as discussed in paragraph **6e**, are 0.021×10^{-3} mg/L and 0.171×10^{-3} mg/L or 0.021 and 0.171 parts per billion, respectively. Thus, both drug substances qualify as a Tier 0 drug substance as both MEECs are less than 1 ppb.

According to CDER's guidance document, a Tier 0 classification relieves the new drug applicant from submitting environmental fate and effects information.

ACCEPTABLE

8-11

According to CDER's guidance document, a Tier 0 classification relieves the new drug applicant from submitting environmental fate and effects information (Format Items 7, 8) and information regarding resource and energy use, mitigation and alternatives (Format Items 9 10, ll)

ACCEPTABLE

12. List of Preparers

Patricia S. Bartholomew
Director, Environmental Affairs
Baxter Healthcare Corporation

Marcia Marconi
Vice President, Regulatory Affairs
Baxter Healthcare Corporation

Craig Seyfried
Director, Environmental Control
Wyeth-Ayerst Laboratories

Oliver Z. Liu
Environmental Scientist
Wyeth-Ayerst Laboratories

ACCEPTABLE

13. Certification

Marcia Marconi, Vice President, Regulatory Affairs, Baxter Healthcare Corporation (January 23, 1997) and Craig F. Seyfried, Director, Environmental Control, Wyeth-Ayerst Laboratories (January 14, 1997) signed the certification as to the truth, accuracy and completeness of the document on the dates in parenthesis.

ACCEPTABLE

14. References

1. Pharmaceutical Manufacturers Association, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA*. July, 1991.

2. U. S. Food and Drug Administration, *Environmental Technical Assistance Handbook*, PB87-175345, U.S. Department of Commerce National Technical Information Service, Springfield, VA. 1987

3. Center for Drug Evaluation and Research, *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, Nov. 1995

4. Environmental Assessment Statement, Sterile Piperacillin/Tazobactam (New Drug Application 50-684), American Cyanmid Company, August, 1991.

ACCEPTABLE

15. Appendices

NON-CONFIDENTIAL

Appendix A. Drug Product Manufacturer's Operating Permit Information

Appendix B. Preparers' Resumes

Appendix X. MSDS's for Drug Substances (not included in Original Submission)

CONFIDENTIAL

Appendix C. Drug Product Information

Appendix D. Five-Year Market Estimates

Appendix E. Expected Introduction Concentration (EIC) Calculation

ACCEPTABLE

/S/

7-1-97
DATE

PREPARED BY
Milton J. Sloan, Ph. D.
Review Chemist
ONDC, Chemistry Division III

/S/

7-1-97
DATE

DIVISION CONCURRENCE
David B. Katague, Ph. D.
Team Leader
ONDC, Chemistry Division III

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

PHARMACOLOGY REVIEW(S)

5-20

MAR 27 1997

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA: 50-750

DRUG: Zosyn (Galaxy Containers)

SPONSOR: Wyeth-Ayerst Laboratories
P. O. Box 8299
Philadelphia, PA 19101

CONTACT PERSON: Karel F. Bernady, Ph.D.
Director, Marketed Products
Phone 610-902-3760

NUMBER OF VOLUMES: 13

DATE OF SUBMISSION: February 24, 1997

DATE CDER RECEIVED: February 24, 1997

DATE ASSIGNED: February 28, 1997

DATE REVIEW STARTED: March 20, 1997

DATE FIRST DRAFT COMPLETED: March 20, 1997

DATE REVIEW ACCEPTED BY TEAM LEADER: March 21, 1997

INTRODUCTION/OVERVIEW

This NDA was submitted to request permission to market a new formulation of an already approved product (Zoysn, NDA 50-684). The new formulation will be marketed in a new container (Galaxy Plastic Containers).

The only significant difference between the approved product and the new product is a slightly higher level of residual
The approved product contains up to 0.6% w/w of
whereas the new formulation will contain up to % w/w of

CONCLUSIONS/RECOMMENDATIONS TO SPONSOR

is classified by the FDA as "generally recognized as safe" (GRAS) and is used in foods as a flavoring agent. is metabolized to There is no reason to believe that the slightly higher levels of in the new formulation would pose any safety concern.

Approval of this NDA is recommended.

/S/

Kenneth Seethaler, Ph.D., D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: Original NDA 50-750
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/R.Alivisatos
HFD-520/Micro/J.King
HFD-520/Chem/M.Sloan
HFD-520/CSO/S.Trostle
HFD-520/Biopharm/H.Sun
HFD-520/Biostat/D.Lin

Concurrence Only:
HFD-520/L.Gavrilovich
HFD-520/R.Osterberg

3/21/07

3/27/07

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

STATISTICAL REVIEW(S)

Statistical Review and Evaluation APR 30 1997

NDA: 50-750

Applicant: Wyeth Ayerst Laboratories

Name of Drug: Zosyn® in Galaxy® Containers

Indications: Treatment of patients with moderate to severe infections caused by piperacillin resistant, piperacillin/tazobactam susceptible, β-lactamase producing strains of microorganisms.

Documents Reviewed: Volumes 1.1 and 1.13, stamp dated February 24, 1997.

Statistical Reviewer: Daphne Lin, Ph.D., HFD-725

Medical Officer: Regina Alivisatos, M.D., HFD-520
Project Manager: Steve Trostle, HFD-520

I. INTRODUCTION

Zosyn® in the vial dosage forms is currently approved under NDA 50-684 for the treatment of patients with moderate to severe infections caused by Piperacillin resistant, Piperacillin/Tazobactam susceptible, beta lactamase producing strains of the designated microorganism. The sponsor, Lederle Piperacillin Incorporated (After June 1, 1995, Wyeth-Ayerst Lab.) has submitted a new NDA in order to obtain approval to market Zosyn® in Galaxy® containers. Zosyn® in Galaxy® containers (PL 2040 Plastic) will be available in three different dosage strengths including 2.25 g/50 mL, 3.375 g/50 mL and 4.5 g/100 mL. The formulation objective was to develop a frozen, premixed product that when thawed would have the equivalent drug composition to the reconstituted, marketed freeze-dried products. This submission is a full new drug application that contains a clinical study. This clinical study was not intended to assess either efficacy or safety, but was intended solely to evaluate the subjective complaint of the frequency and severity of pain on infusion. The pivotal clinical studies assessing efficacy and safety are contained in approved NDA 50-684 for Zosyn®.

II. EVALUATION:

II.A Methods

This was a randomized, double blind, third party unblinded, cross over design study that was designed to compare the subjective complaint of pain on infusion of Zosyn® vial product and premixed Zosyn® product. . Forty normal subjects (20 males and 20 nonpregnant women) were to compete study intervals 1 and 2 in a cross-over design as follows:

Group	Number of Subjects	Interval 1	Interval 2
1	10	4.5g/50 mL vial	3.375 g/50 mL premixed
1	10	3.375g/50 mL premixed	4.5 g/50 mL vial
2	10	4.5g/100 mL vial	4.5 g/100 mL premixed
2	10	4.5g/100 mL premixed	4.5 g/100 mL vial

Each subjects was monitored for pain for 60 minutes. They were asked if they experience pain at 0, 15, 30, 45, and 60 minutes. If a subject experienced pain, then they were asked to describe the pain on a scale from 0 (low) to 10(high). All subjects completed the study except for subject 38 who only completed interval 1 of the study and did not complete interval 2 because this subject tested positive for Cannainoids at interval 2.

The Mainland-Gart test (McNemar, Q, Note on the sampling error of the difference between correlated proportions or percentages, Psychometrika, 12, 153-7, 1947) was applied to check for period interaction or carryover effects. If there are no carryover effects, then McNemar's test is used to test for treatment effects. The sponsor also used Fisher's Exact test to determine if there were differences between the vial and premixed products for whether or not a subject had pain. A t-test was used to determine if there were differences in the amount of pain.

II.B. Results

The sponsor has conducted four different type of analyses: product comparison, concentration comparison, week (time of report pain) comparison, and gender comparison.

Forty subjects entered the study. All forty completed interval 1 of the study and 39 completed both intervals. Of the 40 subjects in the study, 6 experienced pain on infusion at one of the 5 time points. Five subjects (5 of 39, 12.8%) using the premixed product and 2 subjects (2 of 40, 5%) using the vial product experience pain. Table 1 listed the results. The sponsor indicated that the p-value for Fisher's exact test was 0.26, indicating that there was not enough evidence to conclude that there was a significant difference in pain on infusion between the two types of products. Based on a scale from 0 to 10, the average level of pain experience by the subjects was 1.5 with the vial product and 3.0 with the premixed product. There was no significant difference in the intensity of pain between the two groups. (P = 0.13).

For the concentration comparison, one subject (5%) in group 2 experienced pain (pain level of 5) during infusion of the premixed product. In group 1, five subjects (25%) experienced pain, reported a mean pain level of 2.3, with a range of 1-3. One subject experienced pain while using the vial product, three subjects experienced pain while using the premixed product and one subject experienced pain using both products. The differences between these were not significantly different (p = 0.18). Table 2a and 2b summarizes the amount of pain each subject experienced receiving the vial or premixed products.

For the week comparison, the sponsor indicated that there was no significant difference in the

frequency of pain (p = 0.87) or the amount of pain (p = 0.19) between the time periods. Table 3 summarizes the frequency and the amount of pain experienced by subjects by time period.

For the gender comparison, Table 4 summarizes the frequency and the amount of pain experienced by each gender. One male (5%) and 5 females (25%) experienced pain. There is no significant difference in the frequency of pain between the genders (p = 0.18). Table 5 lists all subjects who experience pain. Excluding the subjects experienced pain at just time zero, then there are only three women reported pain while receiving medication.

III. CONCLUSIONS

The sponsor, Wyeth-Ayerst Laboratories, has conducted a clinical study to determine if there is a difference between the Zosyn® vial product and the proposed premixed Zosyn® product in the frequency and severity of the subjective complaint of pain on infusion using two different concentrations of the premixed products.

Forty subjects entered the study. The results showed that there were no significant differences between the vial and premixed products in either the frequency or the amount of pain. There were no significant differences between group 1 (the piperacillin concentrations being compared were 5.7% to 6.0%) and group 2 (the piperacillin concentrations being compared were 3.3% to 4.0%) in the frequency of pain. There were no significant differences in the time periods in either the frequency or amount of pain.

The reviewer agrees with the sponsor's conclusion.

/S/

4/30/97

Daphne Lin, Ph.D.
Team Leader, DBIV

Concur: /S/

Ralph Harkins, Ph.D.
Division Director, DBIV

cc: Archival NDA 50-750
HFD-520
HFD-520/Dr. Alivisatos
HFD-520/Dr. Leissa
HFD-520/Mr. Trostle
HFD-725/Dr. Harkins
HFD-725/Dr. Lin
HFD-725/Chron
This review contains 6 pages and 5 Tables.
WordPerfect 6.1/Zosyn.wp6/4/25/97

Table 1: Summary of Subjects Who Experienced Pain

Concentration	Treatment Group	Pain on Infusion: No Number	No Percent	Yes Number	Yes Percent
Group 1	4.5 g/50ml Vial	18	90.0	2	10.0
	3.375 g/50ml Premixed	16	80.0	4	20.0
Group 2	4.5 g/100ml Vial	20	100.0	.	.
	4.5 g/100ml Premixed	18	94.7	1	5.3

Table 2a: Summary of the Amount of Pain

Treatment Group	N	Mean	Standard Deviation	Min	Max
4.5 g/50ml Vial	2	1.5	0.7	1	2
3.375 g/50ml Premixed	5*	2.6	0.5	2	3
4.5 g/100ml Vial	0	.	.	.	.
4.5 g/100ml Premixed	1	5.0	.	5	5
Vial	2	1.5	0.7	1	2
Premixed	6	3.0	1.1	2	5

* One subject experienced pain at two time periods.

Table 2b: Summary of the Maximum Amount of Pain On a Per Subject Basis

Treatment Group	N	Mean	Std Dev	Difference Mean	Difference Std Dev	Difference p-value
4.5 g/50ml Vial	20	0.2	0.5	.	.	.
3.375 g/50ml Premixed	20	0.5	1.1	0.4	1.1	0.17
4.5 g/100ml Vial	20	0.0	0.0	.	.	.
4.5 g/100ml Premixed	19	0.3	1.1	0.3	1.1	0.33
Vial	40	0.1	0.3	.	.	.
Premixed	39	0.4	1.1	0.3	1.1	0.09

Table 3: Summary of Frequency and Level of Pain by Time

Time	Pain on Infusion No Number	Pain on Infusion No Percent	Pain on Infusion Yes Number	Pain on Infusion Yes Percent	Mean Pain Level
0	37	92.5	3	7.5	2.0
15	39	97.5	1	2.5	1.0
30	38	95.0	2	5.0	4.0
45	39	92.5	1	2.5	3.0
60	39	92.5	1	2.5	3.0

Table 4: Effect of Gender of Pain

Gender	Pain on Infusion: No — Number	No — Percent	Yes — Number	Yes — Percent	Mean Pain Level
Female	15	75.0	5	25.0	2.7
Male	19	95.0	1	5.0	2.0

Table 5: Listing of Subjects With Pain

xter ID	Gender	Interval	Treatment Group	Time	Level of Pain
6	Female	2	4.5 g/50ml Vial	0	2
8	Female	2	4.5 g/100ml Premixed	30	5
17	Female	2	3.375 g/50ml Premixed	0	2
18	Female	1	3.375 g/50ml Premixed	30	3
20	Female	1	4.5 g/50ml Vial	15	1
		2	3.375 g/50ml Premixed	45	3
				60	3
36	Male	2	3.375 g/50ml Premixed	0	2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

MICROBIOLOGY REVIEW(S)

TROSYN
520

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1

MAR 20 1997

NDA # 50-750 **DATE COMPLETED: 19 March, 1997**

APPLICANT(NDA):

Lederle Piperacillin, Inc.
170 Radnor-Chester Road
Radnor, PA 19087

CHEM/THER. TYPE:
Beta-lactam antibiotic

SUBMISSION REVIEWED: Original NDA
PROVIDING FOR: Frozen solution in PL2040 bags

PRODUCT NAMES(S):
Proprietary: Zosyn

Non-Proprietary/USAN: Piperacillin-tazobactam

DOSAGE FORMS(S)
Parenteral
STRENGTHS:
2g/0.25g; 3g/0.375g; and 4g/0.5g

ROUTE(S) OF ADMINISTRATION:
Injectable

PHARMACOLOGICAL CATEGORY:

Antimicrobial

DISPENSED: X Rx ___ OTC

INITIAL SUBMISSION:
Received by CDER: 24 February, 1997
Received by Reviewer: 18 March, 1997
Review Completed: 19 March, 1997

AMENDMENT(S)
Received by CDER: N/A
Received by Reviewer:
Review Completed:

REMARK(S):

This NDA provides for a new dosage form of piperacillin/tazobactam. The new dosage form is a frozen solution of piperacillin/tazobactam. This piperacillin/tazobactam will be used to treat the identical indications associated with the piperacillin/tazobactam dosage form which needs to be reconstituted prior to administration. This new dosage form should have a Microbiology subsection of the package insert identical to the previously marketed product. The draft package insert in this application appears to be identical from the microbioloigical perspective. The application is approvable.

CONCLUSIONS and/or RECOMMENDATIONS:

From the microbiological perspective, this application is approvable.

/S/

James R. King
Reviewing Microbiologist

SMicro/ASheldon

DepDir/LGavrilovich

cc: Orig. NDA # 50-750
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon TD 3/19/97
HFD-502
HFD-520
HFD-520/Micro/King
HFD-520/MO/Leissa
HFD-520/Pharm/Seethaler
HFD-520/Chem/Sloan
HFD-520/CSO/Trostle

Printed for signatures prior to TL review 3/19/97

HFD 520/ TRO54.

JAN 16 1998

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #2

NDA # 50-750 **DATE COMPLETED: 28 July, 1997**

APPLICANT(NDA):

Lederle Piperacillin, Inc.
170 Radnor-Chester Road
Radnor, PA 19087

CHEM/THER. TYPE:
Beta-lactam antibiotic

SUBMISSION REVIEWED: Original NDA
PROVIDING FOR: Frozen solution in PL2040 bags

PRODUCT NAMES(S):
Proprietary: Zosyn

Non-Proprietary/USAN: Piperacillin-tazobactam

DOSAGE FORMS(S)
Parenteral

ROUTE(S) OF ADMINISTRATION:
Injectable

PHARMACOLOGICAL CATEGORY:

Antimicrobial

DISPENSED: X Rx ___ OTC

INITIAL SUBMISSION:
Received by CDER: 24 February, 1997
Received by Reviewer: 18 March, 1997
Review Completed: 19 March, 1997

AMENDMENT(S)
Received by CDER: N/A
Received by Reviewer:
Review Completed:

REMARK(S):
This review is being written to reflect an issue overlooked in the initial NDA review of this application. The NDA provides for a new dosage form of piperacillin/tazobactam. The new dosage form is a frozen solution of piperacillin/tazobactam. This piperacillin/tazobactam will be used to treat the identical indications associated with the piperacillin/tazobactam dosage form which needs to be reconstituted prior to administration. This new dosage form was originally recommended to have a Microbiology subsection of the package insert identical to the previously marketed product. The draft package insert in this application was identical to the previously marketed product from the microbiological perspective. The outstanding issue is discussed below.

Previous reviews of Zosyn dosage forms are not clear about the piperacillin resistance status of isolates which qualified for the second list of microorganisms in the package insert. None of the reviews explicitly state that the second list organisms were drawn only from populations of piperacillin resistant isolates. Indeed, most of the second list organisms appear to be drawn from organisms which can be treated with piperacillin alone. This is important because this drug product only carries Indications involving piperacillin resistant, beta-lactamase producing microorganisms. Therefore, the second list should only contain species drawn from collections of isolates which are piperacillin resistant and beta-lactamase producers. Clearly, the second list needs to be updated for all dosage forms of piperacillin/tazobactam to accommodate the precepts of the NDA Holders Letter of 1993. The second list should only contain organisms which are piperacillin resistant and beta-lactamase producers.

CONCLUSIONS and/or RECOMMENDATIONS:

From the microbiological perspective, the Microbiology subsection of the labeling needs to be updated to reestablish the second list of microorganisms; the second list should only include piperacillin resistant beta-lactamase producing organisms. Until the second list is updated according to the precepts of the NDA Holders Letter, the second list should be deleted from the package inserts of the affected products.

MICROBIOLOGY

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. *in vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium has very little intrinsic microbiologic activity due to its very low level of binding to penicillin-binding proteins; however, it is a beta-lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated beta-lactamases at tazobactam levels achieved with the recommended dosing regimen. Piperacillin/tazobactam has been shown to be active against most strains of the following piperacillin resistant, beta-lactamase producing microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

/S/

7/28/97

James R. King
Reviewing Microbiologist

SMicro/ASheldon

DepDir/LGavrilovich

cc: Orig. NDA # 50-750

HFD-520/DepDir/LGavrilovich

HFD-520/SMicro/ASheldon 1/16/98

HFD-520 1/16/98
HFD-520/Micro/King
HFD-520/MO/Dr. ALBUQUERQUE
HFD-520/Pharm/Seethaler
HFD-520/Chem/Sloan
HFD-520/CSO/Trostle

Printed for signatures 28 JUL 97

Trostle

JAN 30 1998 520

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes # 3

NDA # 50-750 **DATE COMPLETED: 29 Jan, 1997**

APPLICANT(NDA):

Lederle Piperacillin, Inc.
170 Radnor-Chester Road
Radnor, PA 19087

CHEM/THER. TYPE:
Beta-lactam antibiotic

SUBMISSION REVIEWED: Original NDA
PROVIDING FOR: Frozen solution in PL2040 bags

PRODUCT NAMES(S):
Proprietary: Zosyn

Non-Proprietary/USAN: Piperacillin-tazobactam

DOSAGE FORMS(S)
Parenteral

ROUTE(S) OF ADMINISTRATION:
Injectable

PHARMACOLOGICAL CATEGORY:

Antimicrobial

DISPENSED: X Rx ___ OTC

INITIAL SUBMISSION:
Received by CDER: 24 February, 1997
Received by Reviewer: 18 March, 1997
Review Completed: 19 March, 1997

AMENDMENT(S)
Received by CDER: 20 JAN 98
Received by Reviewer: 27 JAN 98
Review Completed: 29 JAN 98

REMARK(S):
This review is being written in response to a requested update for the second list of microorganisms in the product package insert. This new dosage form was originally recommended to have a Microbiology subsection of the package insert identical to the previously marketed product. The draft package insert in this application was identical to the previously marketed product from the microbiological perspective. Clinical Microbiology Review #2, however, recommended that the second list be updated to include only piperacillin resistant organisms that are also beta-lactamase producers. The applicant proposed to update the package insert by submitting the data discussed below.

The applicant made a thorough presentation of data published between 1989 and 1996. However, most of the data submitted were not obtained within a reasonably recent time frame for purposes of the NDA Holders Letter of 1993. Indeed, only foreign data remained after elimination of the outdated surveillance studies provided by the applicant. Therefore, these foreign data could not be corroborated with recent domestic surveillance data. Overall, the data provided in this submission do not support updating the second list of microorganisms within the recommendations contained in the NDA Holders letter of 1993.

More importantly, another weakness of the submission relates to the strength of the data which purport to show that piperacillin resistant strains are susceptible to the piperacillin/tazobactam combination. Certainly, populations of piperacillin resistant organisms were demonstrated and populations of piperacillin/tazobactam susceptible organisms were shown in many of the publications provided by the applicant. However, none of the publications provided analyses comparing the piperacillin/tazobactam susceptibility of specific isolates with the piperacillin susceptibility of the same isolates in line listings. The publications do not provide an understanding of whether a specific isolate is both piperacillin resistant and a beta-lactamase producer while being susceptible to piperacillin/tazobactam. Based on the data presentation, it is impossible to conclude that any of the proposed second list organisms are both piperacillin resistant and beta-lactamase producers while being susceptible to piperacillin/tazobactam.

From the perspective of intuition, many of the proposed organisms will likely qualify for inclusion in the second list of the package insert. However, the data in this submission do not provide a direct presentation of surveillance

data which show individual beta-lactamase producing isolates with the appropriate pattern of resistance to piperacillin and susceptibility to piperacillin/tazobactam. Since the requisite data are missing, then the proposed list of organisms for the second list can not be approved. The Conclusions and Recommendations from Clinical Microbiology Review #2 are still valid.

CONCLUSIONS and/or RECOMMENDATIONS:

From the microbiological perspective, the Microbiology subsection of the labeling still needs to be updated to reestablish the second list of microorganisms; the second list should only include piperacillin resistant beta-lactamase producing organisms which are susceptible to piperacillin/tazobactam. Entries in the second list should be supported by surveillance data shown as line listings of individual isolates which meet these inclusion criteria. The line listings should be grouped according to their appropriate taxonomic categories.

/S/

James R. King
Reviewing Microbiologist

SMicro/ASheldon 1/30/98

DepDir/LGavrilovich

cc: Orig. NDA # 50-750

HFD-520/DepDir/LGavrilovich 2/2/98

HFD-520/SMicro/ASheldon
HFD-520
HFD-520/Micro/King
HFD-520/MO/MAlbuerne
HFD-520/Pharm/Seethaler
HFD-520/Chem/Sloan
HFD-520/CSO/Trostle

Printed for signatures 1-29-98

JUN 10 1997

REVIEW TO HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF NDA
June 10, 1997

A. 1. **NDA 50-750** APPLICANT: **Lederle Piperacillin, Inc.**
170 Radnor-Chester Road
Radnor, PA 19087

2. **PRODUCT NAMES: Piperacillin Sodium & Tazobactam Sodium Injection**
Zosyn® in Galalxy® Containers (PL 2040 Plastic)
3. **DOSAGE FORM:** Intravenous Parenteral in strengths of 2.25g/50mL, 3.375 g/50 mL and 4.5g/100 mL
4. **PHARMACOLOGICAL CATEGORY:** Anti-microbial.
5. **METHOD OF STERILIZATION:** Aseptic Fill

B. 1. **DATE OF INITIAL SUBMISSION:** February 24, 1997
2. **RELATED DOCUMENTS:** DMF
DMF
NDA No. 50-684
NDA No. 50-655
IND
3. **ASSIGNED FOR REVIEW:** March 4, 1997

C. **REMARKS:** This NDA provides for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy ® Containers (PL 2040 Plastic). The drug product is pre-mixed, ready-to-use, frozen dosage form of Zosyn in Baxter's Healthcare Corporation's PL 2040 - Galaxy® Plastic container system and has the same equivalent composition as the reconstituted, marketed freeze-dried product (approved under Lederle Piperacillin, Incorporated NDA 50-684 on October 22, 1993).

D. **CONCLUSIONS:** The NDA 50-750 is not recommended for approval from the standpoint of product quality microbiology.

/S/ 6/10/97

Patricia F. Hughes, Ph.D.
Microbiology Reviewer

cc.: Original NDA 50-750
HFD-160/Consult File
HFD-160/PFHughes
HFD-520/Division File
HFD-520/S.T.Trostle
Drafted by P.F.Hughes/06/10/97
R/D initialed by P. Cooney/06/10/97

PFH 6/10/97

JUL 22 1997

REVIEW TO HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF NDA
July 21, 1997

A. 1. **NDA 50-750** APPLICANT: **Lederle Piperacillin, Inc.**
170 Radnor-Chester Road
Radnor, PA 19087

2. **PRODUCT NAMES: Piperacillin Sodium & Tazobactam Sodium Injection**
Zosyn® in Galalxy® Containers (PL 2040 Plastic)

3. **DOSAGE FORM:** Intravenous Parenteral in strengths of 2.25g/50mL, 3.375 g/50 mL and 4.5g/100 mL

4. **PHARMACOLOGICAL CATEGORY:** Anti-microbial.

5. **METHOD OF STERILIZATION:** Aseptic Fill

B. 1. **DATE OF INITIAL SUBMISSION:** February 24, 1997

2. **DATE OD AMENDMENT:** July 8, 1997

3. **RELATED DOCUMENTS:**
DMF
DMF
NDA No. 50-684
NDA No. 50-655
IND

3. **ASSIGNED FOR REVIEW:** March 4, 1997

C. REMARKS: This amendment contains responses to microbiology deficiencies found in the original NDA submission.

D. CONCLUSIONS: The NDA 50-750 is recommended for approval from the standpoint of product quality microbiology.

/S/ 7/21/97
Patricia F. Hughes, Ph.D.
Microbiology Reviewer

cc.: Original NDA 50-750
HFD-160/Consult File
HFD-160/PFHughes
HFD-520/Division File
HFD-520/S.T.Trostle
Drafted by P.F.Hughes/07/21/97
R/D initialed by P. Cooney/07/21/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 21 1997

NDA 50,750
Zosyn (piperacillin sodium and tazobactam sodium injection)
Original NDA

DATE of SUBMISSION
February 24, 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: Wyeth-Ayerst Research
P.O.Box 8299,
Philadelphia, PA 19101-8299

REVIEWER: HE SUN, Ph.D.

I. RECOMMENDATION

The proposed new drug product is a premixed, ready-to-use, frozen dosage form of marketed Zosyn. The only significant difference between the approved product and the new product is a slightly higher level of residual The approved product contains up to % w/w of whereas the new formulation will contain up tc % w/w of In this submission, Item 6 Human Pharmacokinetics and Bioavailability will be cross-referenced to the previously submitted and approved NDA 50-684 for Zosyn.

is classified by the FDA as "generally recognized as safe" and is used in foods as a flavoring agent. In addition, this is an i.v. dosage form, bioavailability is not a concern. Therefore, the request of waiver the requirement of *in vivo* bioavailability studies by the sponsor should be granted.

/S/ 4/21/97

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. __

cc:
NDA NDA 50,750
HFD-520 (Clinical, CSO)
HFD-340 (Viswanathan)
HFD-880 (Pelsor, Sun)
HFD-880 Div. File NDA 50,750(Zosyn)
CDR (Barbara Murphy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

ADMINISTRATIVE DOCUMENTS

Patent Information

Zosyn is covered by U.S. Patent 4,567,073 which claims the compound Tazobactam. Pursuant to the Certificate Extending patent term under 35 USC 156, issued April 25, 1996, the expiration date of said patent is now February 19, 2007. The owner of the patent is Taiho Pharmaceutical Company, and the applicant is the licensee. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug to which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

Lederle Piperacillin, Inc.

By: _____

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/~~PLA/PMA~~ # 50-750 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Zosyn (piperacillin sodium and tazobactam sodium injection) in Galaxy Containers (PL2040 Plastic) Action: AP AE NA

Applicant Lederle Piperacillin, Inc. Therapeutic Class 3S

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

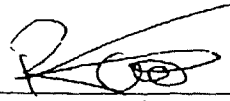
___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ~~ANY OF THE~~ FOREGOING ITEMS, AS NECESSARY.


MD

Signature of Preparer and Title

9/4/98

Date

cc: Orig NDA/PLA/PMA # 50-750
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/30/96)

Zosyn® (piperacillin sodium and tazobactam sodium injection)
in Galaxy® Containers (PL 2040 Plastic)
NDA No. 50-750

ITEM 15 B. Generic Drug Enforcement Act of 1992 Certification Statement

"Wyeth-Ayerst hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food & Drug and Cosmetic Act in connection with application No. 50-750."

Signed: _____

Joseph N. Bathish
Vice President
Worldwide Regulatory Affairs

NO CARCINOGENICITY STUDY(IES) SUBMITTED

DSI AUDIT OF PIVOTAL CLINICAL STUDIES NOT REQUIRED PER MEDICAL OFFICER

APPROVAL LETTER WILL SERVE AS
DIVISION DIRECTOR'S MEMO

SEE MEDICAL REVIEW FOR
SAFETY UPDATE REVIEW

NO ADVISORY COMMITTEE MEETING MINUTES

NO FEDERAL REGISTER NOTICES;
NO OTC OR DESI DOCUMENTS

ADVERTISING MATERIAL
TO BE REQUESTED IN ACTION LETTER

805

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: DAN Boring, Ph.D.

FROM: Division of Anti-Infectives HFD- 520
Attention: MILTON SLOAN Phone 7-2182

DATE: 5-19-97

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: ZOSYN®,TM NDA/ANDA#: 50-750

Company Name: Lederle Piperacillin Inc

Established name, including dosage form: Piperacillin Sodium and Tazobactam Sodium combination parenteral (-2.25g; 3.375g + 4.5

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Treatment of severe infections caused by piperacillin resistant, piperacillin/tazobactam susceptible, β-lactamase producing strains of the designated microorganisms

Initial comments from the submitter: (concerns, observations, etc.)
NDA proposed premixed, ready-to-use, frozen dosage form of Zosyn in Baxter Galaxy® Plastic container system -

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

Consult #805 (HFD-520)

ZOSYN piperacillin sodium and tazobactam parenteral

The name ZOSYN is used for an already approved product containing the noted antibiotics in a different formulation. There is no reason to find the use of the proprietary name unacceptable when applied to the current product.

/S/ 7/16/97, Chair
CDER Labeling and Nomenclature Committee

HFD-520
Trostle

NDA 50-750

MAR 6 1997

Lederle Piperacillin, Inc.
Attention: Karel F. Bernady, Ph.D.
170 Radnor-Chester Road
Radnor, Pennsylvania 19087

Dear Dr. Bernady:

We have received your new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Zosyn (piperacillin sodium and tazobactam sodium injection) in Galaxy Containers (PL 2040 Plastic)
Therapeutic Classification:	Standard
Date of Application:	February 24, 1997
Date of Receipt:	February 24, 1997
Our Reference Number:	50-750

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act on April 25, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Mr. Stephen Trostle, Consumer Safety Officer, at (301) 827-2125.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 3/4/97

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:

Original NDA 50-750
HFD-520/Div. Files
HFD-520/CSO/STrostle
HFD-520/TL/MO/BLeissa
HFD-520/ATL/Chem/DKatague
HFD-520/Chem/MSloan
HFD-520/TL/Pharm/ROsterberg
HFD-520/Pharm/KSeethaler
HFD-520/TL/Stat/DLin
HFD-880/TL/Biopharm/FPelsor
HFD-880/Biopharm/HSun
DISTRICT OFFICE

Drafted by: stt/February 28, 1997\n50750ac.000
Final: stt/March 3, 1997 ST 03/03/97

ACKNOWLEDGEMENT (AC)

Ms. Trostle

MEMORANDUM OF MEETING

NDA 50-750 August 4, 1997
Zosyn (piperacillin sodium and tazobactam sodium)
in Galaxy Containers (PL 2040 Plastic)
Lederle Piperacillin, Inc.

FDA Attendees:
Gary Chikami, M.D., Acting Division Director, Division of Anti-Infective Drug Products (DAIDP), HFD-520
Mercedes Albuerne, M.D., Team Leader, Medical Officer, DAIDP, HFD-520
David Katague, Ph.D., Team Leader, Chemist, DAIDP, HFD-520
Milton Sloan, Ph.D., Chemist, DAIDP, HFD-520
Albert Sheldon, Ph.D., Team Leader, Microbiologist, DAIDP, HFD-520
Richard King, Ph.D., Microbiologist, DAIDP, HFD-520
Frank Pelsor, Ph.D., Team Leader, Biopharmaceuticist, Division of Pharmaceutical Evaluation III (DPEIII), HFD-880
He Sun, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Stephen Trostle, Consumer Safety Officer, DAIDP, HFD-520

Type of meeting:
First labeling meeting for a pending application.

Background material:
Draft package insert, container labels, and carton labels.

Discussion:
The sections and subsections of the labeling to be revised, including the person responsible for follow-up, are as follows:

DESCRIPTION

CLINICAL PHARMACOLOGY

Microbiology

INDICATIONS AND USAGE

PRECAUTIONS
Pregnancy

CSO is to confirm that the reviewing pharmacologist has no comments regarding this section.

DOSAGE AND ADMINISTRATION

REFERENCES

Update the first and third references - Dr. Albuerne

Make editorial changes to the fourth reference - Dr. Albuerne

Action items:

- Regarding the second list in the **Microbiology** subsection, ask the firm to provide the *in vitro* data only for piperacillin resistant and β-lactamase producing organisms.

  On August 6, 1997, CSO conveyed the microbiologist's request for *in vitro* data to Mr. Gary Lewis of the firm.

- CSO is to confirm that the reviewing pharmacologist has no comments regarding the **Pregnancy** subsection.

  On August 4, 1997, CSO confirmed with Dr. Kenneth Seethaler, Reviewing Pharmacologist, that the **Pregnancy** subsection is acceptable.

Minutes preparer: /S/

Stephen T. Trostle, CSO

cc: NDA Arch (50-750)
HFD-520
HFD-520/TL/MO/MAlbuerne
HFD-520/MO/MMakhene
HFD-520/TL/Chem/DKatague
HFD-520/Chem/MSloan
HFD-520/TL/Micro/ASheldon
HFD-520/Micro/RKing
HFD-520/TL/Pharm/ROsterberg
HFD-520/Pharm/KSeethaler
HFD-880/TL/Biopharm/FPelsor
HFD-880/Biopharm/HSun
HFD-520/CSO/STrostle

For concurrence only:
HFD-520/C/PMS/JBona 8/7/97
HFD-520/TL/MO/MAlbuerne 8/7/97
HFD-520/ActgDivDir/GChikami 8/7/97

Draft: stt/08/05/97 \n50750mm.002
Final typed: stt/08/06/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-750

CORRESPONDENCE

WYETH-AYERST RESEARCH

U.S. REGULATORY AFFAIRS

ORIGINAL

February 17, 1998

NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection)
in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic).

Additional reference is made to the Agency's facsimile of February 5, 1998, wherein we were informed of the Agency's draft comments on labeling submitted to NDA 50-750.

Submitted herewith is our response to the Agency's draft comments on proposed labeling. Our comments are attached, listed by labeling section. We appreciate the Agency's review of our comments, and look forward to prompt approval of NDA 50-750.

Please contact the undersigned at (610) 902-3771 (fax 610-964-5972) regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products I
U.S. Regulatory Affairs

WYETH-AYERST *RESEARCH*

U.S. REGULATORY AFFAIRS

February 10, 1998

NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection)
in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic).

Additional reference is made to the Agency's facsimile of February 5, 1998, wherein we were informed of the Agency's draft comments on labeling submitted to NDA 50-750. Further reference is made to recent conversations between the undersigned and Mr. Steve Trostle of the Agency, regarding both the Agency's aforementioned draft labeling comments and on proposed Changes Being Effected Supplements to be sent to the manufacturers of penicillin combination products.

We wish to inform you that we do not accept, in their entirety, the Agency's draft comments on the proposed Zosyn Galaxy labeling, and therefore, we hope to initiate labeling discussions.

We are particularly concerned with the Agency's direction to delete the list from the Microbiology subsection of the Clinical Pharmacology section of Zosyn Galaxy labeling. We understand this action is a result of an unofficial Division policy for all penicillin combination antibiotic drugs to that intends to allow only parent-resistant/combination sensitive, beta-lactamase-producing organisms to be included in this subsection. We also understand that this policy is to be formalized by letter to respective manufacturers at the time an approval letter or complete response letter on the Zosyn Galaxy NDA issues. Further, we understand (personal communication) that the Agency had communicated similar comments to SmithKline Beecham for a pediatric use supplement regarding their Timentin product (approved December 11, 1997), and that the Agency withdrew comments regarding the Microbiology list prior to approval.

We do not believe the Zosyn Galaxy NDA is being given fair and equitable treatment since the policy intending to limit the ' Microbiology list for this class of antibiotics has not been formally adopted at the Agency. Further, formalizing this policy at the same time the Zosyn Galaxy NDA is approved, via request for a Changes Being Effected Supplement, will still allow our competitors to remain on the market for two months or more with Microbiology labeling that will not be equitable to ours with respect to data justification. We are

particularly concerned that the Agency has determined that labeling for SmithKline Beecham's Timentin did not have to comply with the informal policy prior to approval of a recent supplement.

We therefore respectfully request that justification of the Microbiology list of the Zosyn Galaxy NDA be considered a post-approval commitment. In accordance with 21 CFR 201.57 (b)(2)(i), *in vitro* data for anti-infective drugs may be included in labeling if immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown." In fact, most, if not all, antibiotic drugs list *in vitro* data in labeling, and penicillin combination antibiotics should be held to the same standard and policy that applies to other antibiotic classes. We further believe it is appropriate to list the complete *in vitro* spectrum of anti-infective drugs so that physicians may be appropriately informed, and look forward to discussing this further with you. Please contact the undersigned at (610) 902-3771 (fax 610-964-5972) if there are any questions or comments regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products I
U.S. Regulatory Affairs

DCM/drk.225.doc

WYETH-AYERST RESEARCH

U.S. REGULATORY AFFAIRS

AI
ORIG AMENDMENT
ORIGINAL

January 16, 1998

NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to a Request for Information

Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic).

Further reference is made to an August 6, 1997 telephone conversation between our representative Mr. Gary Lewis and FDA's Mr. Stephen Trostle relative to the Agency's review of the Clinical Pharmacology: Microbiology subsection of the proposed package insert labeling for Zosyn in Galaxy Containers. During the conversation, it was requested that Wyeth-Ayerst provide a list of piperacillin resistant, β-lactamase producing microorganisms in support of the *in vitro* only list (2nd list) in the Microbiology subsection. The Agency also requested *in vitro* data in support of the list of microorganisms.

Submitted herewith is information supporting the Agency's request regarding the *in vitro* section of the Microbiology subsection of labeling. Two lists are provided: Table I lists organisms that are currently listed in the labeling, Table II lists organisms that should be considered for addition to the package insert. All organisms noted in the attached tables are considered pathogens for indicated infections (i.e., appendicitis (complicated by rupture or abscess and peritonitis, uncomplicated and complicated skin and skin structure infections, postpartum endometritis or pelvic inflammatory disease, community-acquired pneumonia, nosocomial pneumonia). As can be seen from the tables, the geometric mean MIC_{90} data listed shows that the inhibition of β-lactamase

by tazobactam sodium has conferred piperacillin sensitivity to organisms that were previously considered piperacillin resistant.

The data in the two tables are compiled from 21 different studies published from 1989-1996. The MIC_{90}s of various numbers of isolates have been combined to calculate a geometric mean. Only studies with MIC values, and a fixed tazobactam concentration of 4 μg/mL were included in the compilation. In addition, species with lower numbers of isolates were combined with other members of the genus that met the inclusion criteria (such as *Providencia spp.*, *Peptostreptococcus* spp., *Prevotella* spp. and *Fusobacterium* spp.) and included in the list. For the convenience of the reviewer, reference numbers are included in the tables, and copies of the publications are attached.

We believe the data support the continued inclusion of all currently-listed bacteria in the Microbiology section of labeling, both in the section supported by clinical trial evidence of susceptibility to Zosyn treatment and in the section supported solely by *in vitro* data.

Should you have any questions regarding this submission, please contact the undersigned at (610) 902-3771 (fax 610-964-5972).

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products
U.S. Regulatory Affairs

026

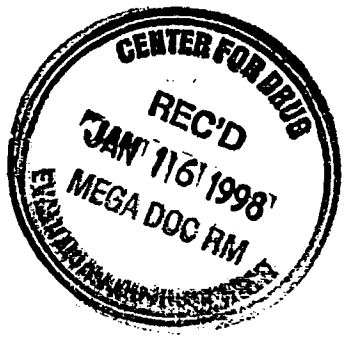
WYETH-AYERST RESEARCH

U.S. REGULATORY AFFAIRS

ORIG MARKED

ORIGINAL BL

January 16, 1998



NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to a Request for Information

Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic).

Additional reference is made to a recent request from Mr. Stephen Trostle of the Agency for an electronic version of the proposed labeling for the aforementioned NDA.

Submitted herewith, attached to the desk copy to Mr. Trostle, is a Word disk containing the proposed labeling for Zosyn® in Galaxy® Containers. Text on the disk is identical to that submitted in the original NDA on February 24, 1997.

Please contact the undersigned at (610) 902-3771 (fax 610-964-5972) if there are any questions or comments regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products I
U.S. Regulatory Affairs

DCM/drk:209.doc

Desk Copy: Mr. S. Trostle

H 138 0

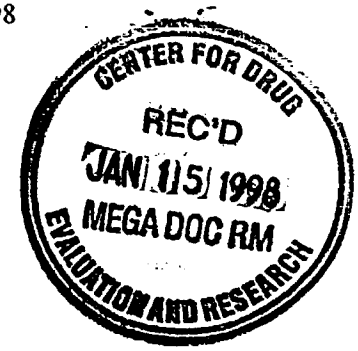
WYETH-AYERST RESEARCH

BC

U.S. REGULATORY AFFAIRS

ORIGINAL

January 14, 1998



NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection)
in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to a Request for Information

Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic).

Additional reference is made to an October 29, 1997 facsimile from the Agency requesting information regarding the qualification of impurity of the ring-opened piperacillin degradation product CL 287,835.

Please be advised that we commit to respond to the Agency's request for information on the qualification of CL 287,836 as a post-approval commitment.

Please contact the undersigned at 610-902-3117 (fax 610-964-5972) if there are any comments or questions regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products I
U.S. Regulatory Affairs

DCM/drk.206.doc

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710 • FAX (610) 964-5973

H 138 O

ORIGINAL BC

CHIC AMENDMENT

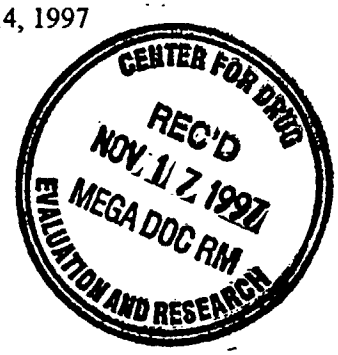
WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

November 14, 1997



NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection)
in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Chemistry Review, Response to FDA's October 29, 1997 Facsimile

Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic). The New Drug Application was submitted on February 24, 1997.

Further reference is made to an October 29, 1997 facsimile (Attachment 1) relative to the chemistry review for Zosyn in Galaxy Containers. The fax consists of two items for which Wyeth-Ayerst is requested to address.

Enclosed, please find our response (Attachment 2) to item #2 of the Agency's October 29, 1997 facsimile. For the convenience of the reviewer, we have reiterated FDA's comments in bold text followed by a response.

Wyeth-Ayerst is continuing to research our records to sufficiently address item #1. A response to item #1 will be provided to the Agency under separate cover at a later date.

Should you have any questions regarding this application, please contact the undersigned at (610) 902-3771 or Mr. Gary Lewis at (610) 902-3788.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products I
U.S. Regulatory Affairs

GML/DCM/drk.89.doc
Desk Copy:
Mr. Stephen Trostle, CSO
Food and Drug Administration

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

July 10, 1997

NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection)
in Galaxy® Containers (PL 2040 Plastic)

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Labeling Review, Response to FDA's July 2, 1997 Facsimile

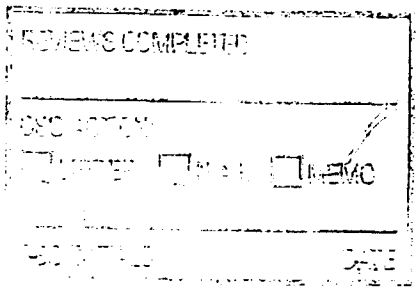
Dear Dr. Chikami:

Reference is made to Lederle Piperacillin Incorporated's pending New Drug Application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic). The New Drug Application was submitted on February 24, 1997.

Further reference is made to a July 2, 1997 facsimile (Attachment 1) which comments on the labeling for Zosyn in Galaxy Containers relative to thawing instructions for the drug product. The fax consists of two items for which Wyeth-Ayerst is requested to address.

Enclosed, please find Baxter Healthcare Corporation's response (Attachment 2) to the Agency's July 2, 1997 facsimile. For the convenience of the reviewer, we have reiterated FDA's comments in bold text followed by a response.

Should you have any questions regarding this application, please contact the undersigned at (610) 902-3771 or Mr. Gary Lewis at (610) 902-3788.



Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione
Director, Marketed Products
U.S. Regulatory Affairs

GML/DCM/drk.055.doc
Desk Copy:
Mr. Stephen Trostle, CSO
Food and Drug Administration

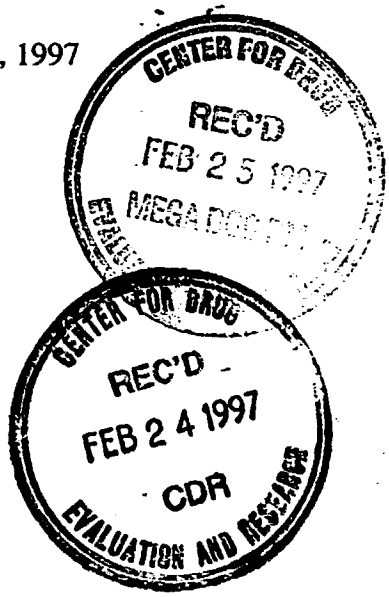
WYETH-AYERST *RESEARCH*

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

February 24, 1997



NDA No. 50-750
Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic)

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Attn: Document Control Room 12B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Feigal:

In accordance with 21 CFR 314.50, Lederle Piperacillin Incorporated hereby submits a new drug application (NDA) for Zosyn® (piperacillin sodium and tazobactam sodium injection) in Galaxy® Containers (PL 2040 Plastic). Effective June 1, 1995, Wyeth-Ayerst Laboratories was appointed to be responsible for all regulatory communications concerning Lederle Piperacillin Inc., and its applications. Further, NDA No. 50-750 and User Fee ID No. 3196 have been preassigned to this application.

The proposed new drug product is a premixed, ready-to-use, frozen dosage form of Zosyn, which utilizes Baxter Healthcare Corporation's PL 2040 Galaxy® Plastic container system. Zosyn in Galaxy Containers (PL 2040 Plastic) will be available in three different dosage strengths including 2.25 g/50 mL, 3.375 g/50 mL and 4.5 g/100 mL. The formulation objective was to develop a frozen, premixed product that when thawed would have the equivalent drug composition to the reconstituted, marketed freeze-dried products. Under the proposed action, the new drug products will have the same indications as Zosyn® in the vial dosage forms currently approved under Lederle Piperacillin, Incorporated's, NDA No. 50-684.

We make reference to NDA No 50-684 for the current approved Zosyn in the vial dosage form for Item 3.I for all information pertaining to the bulk raw material except manufacturers, Item 5 for Nonclinical Pharmacology and Toxicology, Item 6 for Human Pharmacokinetics and Bioavailability, Item 7 for Microbiology and integrated summaries of safety and efficacy which would be contained in Items 8 and 10.

The proposed new drug product is indicated for the treatment of patients with moderate to severe infections caused by piperacillin resistant, piperacillin/tazobactam susceptible, β-lactamase producing strains of microorganisms. Specific indications include: appendicitis complicated by abscesses or rupture and peritonitis caused by *Escherichia coli* or Bacteroides fragilis microorganisms; uncomplicated and complicated infections of the skin and skin structure caused by *Staphylococcus aureus*; postpartum endometritis or pelvic inflammatory disease caused by *Escherichia coli*; moderately severe cases of community-acquired pneumonia caused by Haemophilus influenzae; and nosocomial pneumonia caused by piperacillin-resistant β-lactamase producing strains of *Staphylococcus aureus*.

Please note that in compliance with 21 CFR 314.50(k)(3), and per agreement with our Philadelphia District Office, a true copy of the Chemistry, Manufacturing, and Controls technical sections, plus the application form and summary section of this NDA have been submitted to the Chicago District Office of the FDA, the home office for Baxter's manufacturing facility, at the address below:

Ms. Lorelei Jarrell
Program Coordinator for Field Copy Submissions
Chicago District Office
Food and Drug Administration
300 South Riverside Plaza
5th Floor, Suite 550 South
Chicago, Illinois 60606

To assist in the Agency's administrative coordination of this NDA, we have also provided a copy of the NDA cover letter to the FDA home district office located in Philadelphia, PA. The requested certification concerning this field copy plus the certification required under the Generic Drug Enforcement Act of 1992 are contained in Item 15 of this application. A check for 50% of the required application fee has been submitted to the Pittsburgh postal address designated for user fee payments.

<u>Clinical Study</u>

This submission is a full new drug application that contains a clinical study. This study was not intended to assess either efficacy or safety, but was intended solely to evaluate the subjective complaint of the frequency and severity of pain on infusion. The pivotal clinical studies assessing efficacy and safety are contained in approved NDA No. 50-684 for Zosyn. Due to the inclusion of this clinical study, it was agreed that one half the full user fee payment is required.

NDA Contents

The NDA is organized as follows:

Item No.	Description	Volume Nos.
1	Index	1.1
2	Summary	1.1
3	Chemistry, Manufacturing, and Controls	1.2
4	Methods Validation Package and Draft Labeling	1.8
5	Nonclinical Pharmacology and Toxicology	1.10
7	Microbiology	1.11
8	Clinical	1.12
10	Statistical	1.13
13	Patent and Exclusivity Information	1.1
15a	Certification Required by New Drug and Abbreviated New Drug Applications Preapproval Inspection Requirements	1.1
15b	Certification Required by Generic Drug Enforcement Act of 1992	1.1

Regulatory History

On August 9, 1996, Wyeth-Ayerst submitted a supplemental application (NDA 50-684/S-008) providing for manufacturing changes to the tazobactam drug substance manufacturing process. The supplemental application was approved December 13, 1996. The NDA Stability Batches for the frozen premixed drug product were manufactured with the then current tazobactam manufacturing process material (NDA 50-684/S-007). In accordance with an agreement made

between the Division of Anti-Infective Drug Products and Wyeth-Ayerst during a teleconference on July 22, 1996, one (1) batch of each concentration of Zosyn® injection in PL 2040 Galaxy Plastic Containers has been manufactured by Baxter Healthcare Corporation to evaluate the drug product manufactured using the tazobactam drug substance prepared by the revised process. Stability studies are being conducted in accordance with the commercial product stability protocols identified in Item 3.II.G. The stability data will be reported in NDA annual reports.

Should you have any questions regarding this application, please contact the undersigned at (610) 902-3760 or Mr. Gary Lewis at (610) 902-3788.

Sincerely,

WYETH-AYERST LABORATORIES

Karel F. Bernady, Ph.D.
Director, Marketed Products
U.S. Regulatory Affairs

cc: cover letter w/o attachments
Ms. Debra Pagano
Program Coordinator for Field Copy Submissions
Department of Health and Human Services
Food and Drug Administration
2nd and Chestnut Streets
Philadelphia, PA 19101-2973

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
24 FEB 97	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
520	50-750

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Lederle Piperacillin, Inc.	
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
170 Radnor-Chester Road Radnor, PA 19087	(610) 902-3760
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA No. 50-750

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Piperacillin sodium & tazobactam sodium injection	Zosyn® in Galaxy® Containers (PL 2040 Plastic)

CODE NAME *(If any)*	CHEMICAL NAME
	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-[2α, 5α, 6β,(S*)]]-(2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate-4,4-dioxide

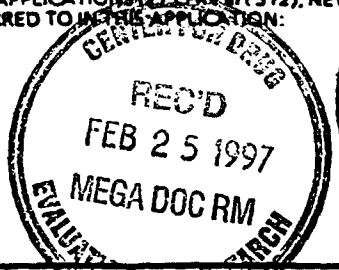
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Parenteral	Intravenous	2.25g/50 mL 3.375g/50 mL 4.5g/100mL

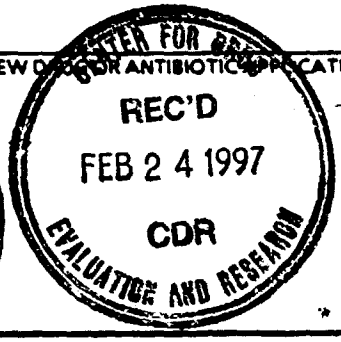
PROPOSED INDICATIONS FOR USE

Zosyn is indicated for the treatment of patients with moderate to severe infections caused by piperacillin resistant, piperacillin/tazobactam susceptible, β-lactamase producing strains of the designated microorganisms.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

DMF
DMF
NDA No. 50-684
NDA No. 50-655
IND





INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*