CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 050608 /S019

Trade Name : UNASYN

Generic Name: Ampicillin/Sulbactam IM/IV

Sponsor : Pfizer, Inc.

Approval Date: February 12, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 050608 /S019

APPROVAL LETTER

02-18-97P01:52 RCVD

NDA 50-608/S-019

Robert B. Clark, Ph.D.
Sr. Associate Director
Regulatory Affairs
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

FEB 12 1997

Dear Dr. Clark:

Reference is made to your November 30, 1993, supplemental new drug application (NDA) and your resubmission dated October 9, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for UNASYN® (ampicillin sodium/sulbactam sodium), IM/IV.

We acknowledge receipt of your amendments to NDA 50-608/S-019 dated March 30, April 7, June 2, and November 16, 1994; and March 13, 1995.

This supplemental application provides for the treatment of skin and skin structure infections for pathogens already in the labeling in pediatric patients

We have completed our review of **NDA 50-608/S-019** supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the treatment of skin and skin structure infections in pediatric patients 1 year of age or older as recommended in the October 9, 1996, draft labeling. 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 October 9, 1996. 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 sixteen 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 50-608/S-019.** Approval of this FPL 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.

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 the Division of Anti-Infective Drug Products 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 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. Steven Trostle
Regulatory Health Project Manager
(301) 827-2125

Sincerely yours,

1-23-97

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Original NDA 50-608
HFD-520/Div. files
HFD-520/S.Trostle
HFD-520/B.Leissa 1/10/97
HFD-520/R.Alivisatos 12/23/96
HFD-104/T.Nearing
HFD-830/E.Sheinin
DISTRICT OFFICE
HFD-2/M.Lumpkin
HFD-101/L.Carter (with labeling)
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling)
HFD-021/J.Treacy (with labeling)
drafted:by PFogarty/Dec. 19, 1996
final:PF/12/20/96
APPROVAL

Concurrence only:

HFD-520/JBona 12/20/96

NDA 50-608/S-019

9.1.96

Robert B. Clark, Ph.D.
Sr. Associate Director
Regulatory Affairs
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Clark:

Reference is made to your November 30, 1993, supplemental new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for UNASYN® (ampicillin sodium/sulbactam sodium), NDA 50-608/S-019.

We acknowledge receipt of your amendments to NDA 50-608/S-019 dated March 30, April 7, June 2, and November 16, 1994; and March 13, 1995.

This supplemental application provides for the treatment of skin and skin structure infections for pathogens already in the labeling in pediatric patients

We have completed our review of NDA 50-608/S-019 supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the treatment of skin and skin structure infections in pediatric patients 1 year of age or older. Therefore, it is approvable with the labeling changes listed below:

CLINICAL PHARMACOLOGY:

1. The last paragraph of this section (immediately before the **Microbiology** subsection) should be revised to read:

2. Please include the for pediatric patients in this section of the labeling.

INDICATIONS AND USAGE:

This section should read as in the labeling submitted with this supplement with one addition. After the indication for **"Skin and Skin Structure infections"** please add the following:

PRECAUTIONS:

The Pediatric Use subsection should be revised to read as follows:

ADVERSE REACTIONS:

Please create two subsections in this section, and entitle them "**Adult Patients**" and "Pediatric Patients." The subsection entitled "**Adult Patients**" should be placed before the ADVERSE REACTIONS section of the current labeling. It should read as follows:

"ADVERSE REACTIONS

The other subsection should read as follows:

DOSAGE AND ADMINISTRATION:

The new proposed paragraph on Infants and Children should be deleted and replaced with the following paragraph:

A CLINICAL STUDIES section should be added to the labeling and be inserted after the OVERDOSAGE section and before the DOSAGE AND ADMINISTRATION section. This section should read as follows:

"CLINICAL STUDIES:

We further concluded that the data submitted to support the use of UNASYN in pediatric patients were inadequate as defined under 21 CFR 314.125(b)(5) and, therefore, it is not approvable at this time. Subsequently, for administrative purposes, we have assigned this indication a new supplement number.

The indication is not approved because there is a lack of substantial evidence consisting of adequate and well-controlled investigation, as further defined in 21 CFR 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed in the proposed labeling.

The data submitted do not support a monotherapy indication, and do not contribute adequate evidence that could be used to grant an indication for with Unasyn plus an aminoglycoside. Despite the small sample size, the efficacy analysis raises concern about the therapeutic equivalence of Unasyn plus an aminoglycoside when compared to the standard triple therapy regimen in this clincial trial.

All future communications regarding Unasyn infections in pediatric patients should be directed to the new supplement number.

In addition, our review of the data submitted in this supplemental application indicates that the Microbiology subsection of the package insert needs to be revised. However, this issue will be addressed in a separate letter.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action, the Food and Drug Administration may take action to withdraw the supplemental application.

In accordance with the policy described in 21 CFR 314.102 (d) of the new drug regulations, you may request an informal conference with members of the Division of Anti-Infective Drug Products to discuss what further steps you need to take to secure approval. The meeting is to be requested at least 15 days in advance.

The changes regarding the use of UNASYN in pediatric patients with Skin and Skin Structure infections may not be implemented until you have been notified in writing that this supplemental application (NDA 50-608/S-019) is approved.

If you have questions, please contact:

Ms. Pauline Fogarty
Regulatory Health Project Manager
(301) 827-2125

Sincerely yours,

David W Feigal 9.11.95

David W. Feigal, Jr., M.D., MPH
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:orig NDA 50-608
HFC-130/JAllen
HFD-80
HFD-520
HFD-520/Act.Div.Dir/DFeigal
HFD-520/MO/HHamilton
HFD-520/TL/BLeissa
HFD-520/Micro/PDionne
HFD-520/TL/ASheldon
HFD-521/PM/PFogarty
PF8/20/96//9/11/96 9/11/96

Concurrence only:
HFD-520/TL/RRoberts 9/12/96

HFD-521/CPM/JBona

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 050608

ADMINISTRATIVE DOCUMENTS

HFD-520
Fogarty

LABELING REVIEW
NDA 50-608/SUPPLEMENT S-019
UNASYN
(AMPICILLIN/SULBACTAM SODIUM)
SUPPLEMENT FOR PEDIATRIC PATIENTS

This labeling review will address the labeling changes considered necessary after completed review of data submitted in the pediatric supplement (S-019) to the NDA 50-608. The labeling found in the 49th edition of the Physicians' Desk Reference (1995) is considered the current labeling.

Changes to the labeling considered necessary by the medical officer are reviewed below. The format and content of these changes are based on guidance provided in the Federal Register, 21 CFR Part 201, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule", December 13, 1994. Labeling changes recommended by reviewers from Biopharmaceutics and Microbiology have also been incorporated into the summary labeling changes recommended below.

DESCRIPTION

No changes are requested or necessary in this section.

CLINICAL PHARMACOLOGY

The applicant is requesting the following in the CLINICAL PHARMACOLOGY Section of the package insert:

As noted by Dr. He Sun, Clinical Pharmacology and Biopharmaceutics reviewer, the C_{max} value reported from U.S. studies varies from mcg/mL for ampicillin, and mcg/mL for sulbactam, and the proposed labeling should be changed to be consistent with the data reported. Thus, the labeling should be amended as shown below:

The applicant should also provide the AUC, above MIC and C_{max}/MIC ratios for pediatric patients in this subsection of the labeling.

MICROBIOLOGY

The annotated package insert included in the submission makes no changes to the **MICROBIOLOGY** subsection. However, this section of the label is outdated, and does not conform to present labeling requirements. The following revisions are taken directly from the microbiology review by Peter Dionne; some nonsubstantive editing changes may be required for this section prior to final labeling approval:

1. [redacted] should be deleted from the label since no data have been submitted in this submission for this organism.

2. [redacted] should not be added to the label since data from only one study with 22 isolates were submitted.

3. [redacted] should be deleted from the label since data for only 2 isolates were submitted.

4. [redacted] should not be added to the label since the MIC_{90} values in the submitted studies were above the [redacted] µg/mL susceptible breakpoint.

5. [redacted] should be deleted from the label since only two studies with 21 isolates total have been submitted in this submission for this organism.

6. [redacted] should be deleted from the label since only one study with 19 isolates and a high MIC_{90} value has been submitted.

7. [redacted] should be deleted from the label since only one study with 20 isolates and a high MIC_{90} value has been submitted.

8. [redacted] should be deleted from the label since only one study with 20 isolates and a high MIC_{90} value has been submitted.

9. [redacted] should be deleted from the label since only one study with 20 isolates and a high MIC_{90} value has been submitted.

). [redacted] should be deleted since the only current species is [redacted] which is not usually a pathogen. No data were submitted for this organism.

11. The 'Microbiology' subsection of the label should be updated to conform with the way this section is written at the present time. This includes separating the listing of organisms into two list; one with both *in vitro* activity and clinical efficacy and a second list with only *in vitro* activity. To be listed in this second listing, usually 100 isolates from various geographical locations across the United States must be tested by NCCLS methods and the MIC_{90} values from these studies must be equal or less than the susceptible breakpoint for these organisms. These organisms must also be potential pathogens in diseases for which the product has an indication.

The susceptibility testing section must also be updated to include new breakpoints and quality control organisms.

The MICROBIOLOGY subsection of the labeling should be revised as shown below:

"MICROBIOLOGY"

The presence of sulbactam in the UNASYN formulation effectively extends the antibiotic spectrum of ampicillin to include many bacteria normally resistant to it. Thus, UNASYN possesses the properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Ampicillin/sulbactam has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

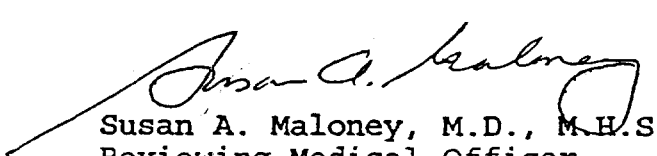
Medical Officer's Comment: Recent microbiologic surveys indicate that most strains of the following gram-negative aerobes are now resistant *in vitro* to Unasyn (ampicillin/sulbactam): *Escherichia coli*, *Enterobacter* species, and *Klebsiella* species. The present labeling is based on clinical efficacy data submitted in the 1980's, before resistance to Unasyn was documented. Therefore, the following revision to the above labeling is appropriate:

** Ampicillin/sulbactam was shown to be active against these microorganisms, both *in vitro* and in clinical infections, in clinical trials performed in the 1980's. Recent microbiologic survey data, however, indicate that most strains of these microorganisms are now resistant to ampicillin/sulbactam *in vitro*. Data documenting the clinical efficacy of ampicillin/sulbactam against organisms with *in vitro* resistance are not available.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ampicillin/sulbactam exhibits *in vitro* minimal inhibitory concentrations (MICs) of μg/mL or less against most (≥90%) strains *Neisseria gonorrhoeae*; MICs of μg/mL or less against most (≥90%) strains of streptococci; MICs of μg/mL or less against most (≥90%) strains of *Haemophilus influenzae*; and MICs of μg/mL or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to ampicillin alone, the safety and effectiveness of ampicillin/sulbactam in treating infections due to these microorganisms have not been established in adequate and well-controlled clinical trails.

Pages 7-13
Deleted
Labeling Revisions



Susan A. Maloney, M.D., M.H.S
Reviewing Medical Officer
Division of Anti-Infective Drug Products

CC: original NDA 50-608
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/Hhamilton
HFD-520/TL/BLeissa
HFD-880/Biopharm/HSun
HFD-520/Micro/PDionne
HFD-520/Chem/SRoy
HFD-520/ProjMng/PFogarty

Concurrence only:
HFD-520/ActDivDir/DFeigal (OK) 9.11.96

HFD-520/TL/RRoberts
RR 8/22/1996

Addendum to Labeling Review for Supplement

Date of addendum: August 1, 1996

NDA/Supplement number: 50-608/S-019

Name of drug: Unasyn (ampicillin sodium/sulbactam sodium)

Applicant: Pfizer Inc.
New York, NY 10017-5755

Subject:
This efficacy supplement was submitted on November 3, 1993, and requested labeling for use of Unasyn in the treatment of skin and skin structure infections in pediatric patients. The medical officer review has been completed by Dr. Susan Maloney in which it was recommended that approval be granted for the use of Unasyn in the treatment of skin and skin structure infections in pediatric patients one year of age or older. However, there was inadequate evidence to recommend approval for Unasyn in the treatment of , non-approval has been recommended.

Dr. Maloney did the initial labeling review for this supplement and incorporated the comments and recommendations of the biopharm reviewer, Dr. He Sun, and the microbiology reviewer, Peter Dionne, into her review. The comments of the biopharm reviewer are specific to the efficacy supplement as they recommend changes in the new "proposed" paragraph in the **CLINICAL PHARMACOLOGY** section of the package insert regarding the pharmacokinetic information in pediatric patients. The recommendations made by the microbiology reviewer, however, are not specific to this efficacy supplement, but rather address updating the entire microbiology section and include information on the susceptibility of more recent isolates that the applicant submitted with the efficacy supplement.

Appropriate sections of Dr. Maloney's signed off clinical review as well as the recommended labeling changes were sent to the applicant, Pfizer, in May 1996. A telecon was held with the applicant on May 21, 1996, to answer questions and get their feedback regarding the proposed labeling. Most of the telecon was directed by the applicant regarding why labeling for use in the treatment of infections in pediatric patients was not being recommended for approval. The revisions to the **Microbiology** subsection were discussed especially the information regarding *in vitro* resistance of ampicillin/sulbactam to several gram-negative pathogens based on the isolate data submitted with the supplement. The applicant, as represented in the telecon, appeared totally unaware these data had been submitted and was unprepared to address this during the telecon. It was requested of the applicant to consider the labeling revisions as specified by the Division and to respond to these. After several weeks there was no response from the applicant and a meeting scheduled with Pfizer for July 30, 1996, was canceled by the applicant. In order to come to closure on this very old outstanding supplement, the appropriate Division members, including Dr. Feigal, the Acting Division Director, met internally.

At the in-house meeting held by the Division on July 30, 1996, it was decided to separate the labeling recommendations into those that are specific to the efficacy supplement which requested information regarding use in the pediatric population from those recommendations that apply to the NDA in general, i.e., the microbiology recommendations.

In addition, since the clinical review team used the final pediatric labeling rule published December 13, 1994, to support its recommendations for the approval of the use of Unasyn in the treatment of skin and skin structure infections in pediatric patients one year of age or older, Dr. Roberts, the secondary reviewer, discussed the language of the labeling with the Pediatric Subcommittee in their meeting on May 28, 1996. Their recommendations were conveyed to Dr. Maloney, however, they were never incorporated into the labeling review prior to Dr. Maloney's departure from the agency in early July, 1996.

The purpose of this **Addendum to the Labeling Review** is to: (1) include only the labeling recommendations that are specific to the supplement, i.e., the biopharm recommendations [**CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections] and the clinical reviewer recommendations [**INDICATIONS AND USAGE**,

PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and **CLINICAL STUDIES** sections]. (The microbiology reviewer recommendations will be conveyed to the applicant separately.); and (2) to incorporate the revisions as recommended by the Pediatric Subcommittee.

Labeling Review

CLINICAL PHARMACOLOGY

1) The last paragraph of this section (immediately before the **Microbiology** subsection) should be revised to read as follows:

2) In addition, please include the for pediatric patients in this section of the labeling.

MICROBIOLOGY

The review/recommendations for this subsection will be conveyed separately to the applicant as noted above.

INDICATIONS AND USAGE

This section should read as in the labeling submitted with the supplement with one addition. After the indication for **Skin and Skin Structure infections** a note should be placed that reads as follows:

PRECAUTIONS

The **Pediatric Use** subsection should be revised to read as follows:

ADVERSE REACTIONS

Two subsections should be created in this section: **Adult Patients** and **Pediatric Patients**. The subheading "**Adult Patients**" should be placed before the **ADVERSE REACTIONS** section of the current labeling. It should read as follows:

"ADVERSE REACTIONS

Adult Patients: Unasyn is generally well tolerated. The following...".

The new subsection should read as follows:

DOSAGE AND ADMINISTRATION

CLINICAL STUDIES

A **CLINICAL STUDIES** section should be added to the labeling and be inserted after the **OVERDOSAGE** section and before the **DOSAGE AND ADMINISTRATION** section. This section should read as follows:

Conclusions/recommendations:
The supplement (NDA 50-608/S-019) is recommended as approvable with the labeling changes as outlined above. It is recommended that Unasyn be approved for use in the treatment of **Skin and Skin Structure Infections** in pediatric patients . The applicant should be notified of these recommended actions.

Rosemary Roberts, MD
Medical Team Leader/HFD-520

cc: original NDA
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/HHamilton
HFD-520/TL/BLeissa
HFD-880/Biopharm/HSun
HFD-520/Micro/PDionne
HFD-520/Chem/SRoy
HFD-520/ProjMng/PFogarty
HFD-520/RRoberts/08-16-96/N50608.S19

Concurrence only:
HFD-520/ActDivDir/DFeigal 9/11/96

Addendum #2 to Labeling Review for Supplement

Date of addendum: September 11, 1996

NDA/Supplement number: 50-608/S-019

Name of drug: Unasyn (ampicillin sodium/sulbactam sodium)

Applicant: Pfizer Inc.
New York, NY 10017-5755

Background:
The first addendum to the labeling review for this supplement was done by the team leader and is dated August 1, 1996. Based on this review, an action letter was written and sent forward to Dr. Feigal for signature. Dr. Roberts, the team leader, met with Dr. Feigal on September 10, 1996, to discuss the letter and the labeling changes to be sent with the action letter to Pfizer. After discussion, it was agreed to make the following changes:

CLINICAL STUDIES section:

1) Delete the subsection

2) In the subsection **Skin and Skin Structure Infections in Pediatric Patients**, delete the

PRECAUTIONS section:
In the second paragraph of the new **Pediatrics Use** subsection, delete the second sentence in parentheses. The second paragraph should read as follows:

Recommendations:

1) The labeling changes to be included in the action letter should be revised with the changes outlined in this addendum.

2) The revised action letter should be forwarded to Dr. Feigal for review and signature.

Note:
The above changes were discussed with Pauline Fogarty, the project manager for Unasyn, this am. She made the changes as outlined during the telecon. She will include these changes in the action letter and forward it to Dr. Feigal.

Rosemary Roberts, MD
Medical Team Leader/HFD-520

cc: original NDA
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/HHamilton
HFD-520/TL/BLeissa
HFD-880/Biopharm/HSun
HFD-520/Micro/PDionne
HFD-520/Chem/SRoy
HFD-520/ProjMng/PFogarty
HFD-520/RRoberts/09-11-96/N50608ad2.s19

Concurrence only:
HFD-520/ActDirDir/DFeigal 9.12.96

MEDICAL OFFICER
MEMORANDUM-TO-THE-FILE

Date: November 26, 1996

NDA 50-608/S-019
Unasyn (ampicillin sodium/Sulbactam sodium) IM/IV
Pfizer Inc.
Submission dated: October 9, 1996

The submission dated October 9, 1996, is the firm's response to our approvable letter dated September 11, 1996. The firm has incorporated all of our labeling changes that we requested in our approvable letter except one in the CLINICAL PHARMACOLOGY section (see Biopharm review).

Recommendation: This supplement should be approved based on the submitted draft labeling.

MD 11/26/96

Regina Alivisatos, M.D.
(Reviewing Medical Officer)

cc: NDA Arch (NDA 50-608/SE5-019)
HFD-520
HFD-520/RAlivisatos/BLeissa/STrostle
/N50608MF.MO BL 11/26/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 050608

MEDICAL OFFICER REVIEW

MEDICAL OFFICER'S REVIEW
NDA: 50-608, SUPPLEMENT NUMBER SE5-019
AMPICILLIN/SULBACTAM SODIUM (UNASYN)
CLINICAL EFFICACY FOR PEDIATRIC PATIENTS

MEDICAL OFFICER'S REVIEW
NDA: 50-608, SUPPLEMENT NUMBER SE5-019
AMPICILLIN/SULBACTAM SODIUM (UNASYN)
CLINICAL EFFICACY SUPPLEMENT FOR PEDIATRIC PATIENTS

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MEDICAL OFFICER'S REVIEW OF NDA 50-608: SUPPL. SE5-019

DATE OF SUBMISSION:	October 30, 1993
DATE RECEIVED BY MEDICAL OFFICER:	August 18, 1994
DATE REVIEW INITIATED:	October 10, 1994
DATE DRAFT #1 (SSTI) TO SUPERVISOR:	February 6, 1995
DATE DRAFT #2 (SSTI) TO SUPERVISOR:	May 1, 1995
DATE DRAFT #3 (IA) TO SUPERVISOR:	October 2, 1995
DATE REVIEW COMPLETED:	January 6, 1996
DATE REVIEW SUBMITTED FOR CONCURRENCE:	January 26, 1996

I. OVERVIEW OF SUPPLEMENT SUBMISSION

APPLICANT: Pfizer Pharmaceuticals, Inc.
235 East 42nd Street
New York, New York 10017

DRUG:

Generic Name: Ampicillin sodium/sulbactam sodium

Trade Name: UNASYN®

Chemical Name: **Ampicillin sodium:** monosodium (2S,5R,6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

Sulbactam sodium: sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide

Molecular Formula: **Ampicillin sodium:** $C_{16}H_{18}N_3NaO_4S$
Sulbactam sodium: $C_8H_{10}NNaO_5S$

Molecular Weight: **Ampicillin sodium:** 371.39

Sulbactam sodium: 255.22

Drug Category: Beta-lactam/beta-lactamase inhibitor

Route of Administration: Parenteral

Dosage Form: Powder for reconstitution/IV or IM injection

How Supplied: As sterile off-white dry powder in glass vials and piggyback bottles

Vials/Bottles: 1.5 g of UNASYN = 1 g ampicillin + 0.5 g sulbactam
3.0 g of UNASYN = 2 g ampicillin + 1.0 g sulbactam

MATERIAL REVIEWED:

- Original 46 volumes containing clinical studies of pediatric patients with skin and skin structure infections,

- Summary of clinical studies conducted outside the United States

Medical Officer's Comment: 58 patients participated in a U.S. noncomparative study of Unasyn in the treatment of periorbital/facial cellulitis (study terminated prematurely due to low enrollment). Data will be used in pharmacokinetic and safety evaluations only.

RELATED IND: IND

PROPOSED LABELING:

4 Pages (4-7)
Deleted
Labeling Revisions

II. REVIEW OF CLINICAL STUDIES

INDICATION: SKIN AND SKIN STRUCTURE INFECTIONS
Protocol: 89CE20-0449

Title: A Multicenter Comparison of 2:1 Ampicillin/Sulbactam (Unasyn) Versus Cefuroxime in the Treatment of Skin and/or Skin Structure Infections of Bacterial Etiology in Hospitalized Pediatric Patients. [Volume 13 (study synopsis) through volume 16]

Study dates: August 16, 1990 -- May 18, 1992

Objective: To compare the safety and efficacy of parenterally administered Unasyn and cefuroxime in the treatment of hospitalized pediatric patients with skin and skin structure infections.

A. STUDY SUMMARY

Design Overview: Open-label, randomized, comparative multicenter study of parallel design.

Method of Patient Assignment: Randomization code was designed to result in assignment of two patients to Unasyn for each patient assigned to cefuroxime.

Inclusion criteria: Males or females age 3 months through 11 years of age who were hospitalized and required parenteral antimicrobial therapy for skin and/or skin structure infections (SSTI) of presumed bacterial etiology. The investigators based their diagnosis of SSTI on findings in the medical history, physical examination, and other appropriate diagnostic findings. At the initial clinical evaluation the patient was required to be classified by the investigator into one or more of the following groups:

(1) Superficial and bullous impetigo
(2) Folliculitis, furunculosis, and carbunculosis
(3) Hidradenitis
(4) Wound infections (surgical or traumatic)
(5) Erysipelas
(6) Cellulitis, including periorbital and facial cellulitis and cellulitis secondary to a viral exanthem
(7) Other

Written informed consent from the parent or legal guardian of each minor patient enrolled in the study was required.

Medical Officer's Comments: Investigators were required to record signs and symptoms consistent with skin or soft tissue infection --redness, swelling, drainage, ulceration, and pain--, however, no minimum criteria for diagnosis of SSTI were specified. Further, specific SSTI diagnoses, i.e., cellulitis, furunculosis, or abscess, were not defined in the protocol. The diagnosis of each patient was left to the discretion of the individual investigator.

Exclusion criteria: Prospective patients were excluded as follows:

1. Had known or suspected hypersensitivity to penicillins

or cephalosporins.

2. Had received successful antimicrobial therapy (as evidenced by either a clinical cure or improvement or eradication of the infecting pathogen) or any parenteral antimicrobials within 48 hours of study entry.

3. Were terminally ill or had an underlying disease thought to have the potential to interfere with evaluation of the efficacy or safety of study drug.

4. Had immunologic (including neutrophil) disorders or cytopenias (leukocyte count < $3000/mm^3$, platelet count < $100,000/mm^3$, hemoglobin less than 8.0 mg/dL).

5. Had clinically significant renal dysfunction (evidenced by one or more of the following: serum creatinine greater than 2.5 mg/dL, BUN greater than 50 mg/dL or estimated creatinine clearance less than 50 mL/min/1.73 m^2 body surface area).

6. Had poorly controlled diabetes mellitus.

7. Had a glycogen storage disease or a strong family history of a glycogen storage disease.

8. Were in a clinical study of another investigational drug or had received another investigational drug within the previous four weeks.

9. Were pregnant, likely to become pregnant, or nursing.

10. Had signs or symptoms of meningitis. All patients 18 months of age or younger with facial (buccal) or periorbital (preseptal) cellulitis, evidence of sepsis or *Hemophilus influenzae* infection were required to have a lumbar puncture to rule out central nervous system infection prior to entry into the study.

11. Were diagnosed (by clinical and/or radiological evaluation) with osteomyelitis or suppurative arthritis.

Study Drugs and Dosage: **Ampicillin/Sulbactam:** 150-300 mg (100-200 mg ampicillin/50-100 mg sulbactam) per kg of body weight (up to maximum of 40 kg), administered daily in equally divided doses every 6 hours via the intravenous or intramuscular route.

Cefuroxime: 50-100 mg/kg administered daily in equally divided doses every 6 to 8 hours via the intravenous or intramuscular route.

Duration of therapy: The maximum period of treatment was based on the investigator's clinical judgment and patient response, but was not to exceed 14 days.

Concomitant medications: With the exception of the optional transitional (oral) medication, no antibiotics other than the study drugs were permitted during the

study.

Transitional therapy (Oral): The investigator had the option of prescribing a course of oral antimicrobial therapy after treatment with parenteral study drug was completed. The use of this type of transitional therapy is common practice in pediatric medicine. The decision to prescribe or omit oral antimicrobial therapy and the choice of oral drug (if any) was made by the investigator; the study protocol provided no criteria for use (or omission) of oral transitional antimicrobials and did not identify any preferred oral drug.

The study protocol did, however, identify objective criteria to be met prior to transition to oral therapy. These criteria were:

(1) A minimum of 72 hours of parenteral therapy
(2) A minimum period of 24 hours afebrile
(3) Improvement/resolution of signs and symptoms of infection

For patients who required transitional oral therapy, susceptibility testing of the original pathogen, if isolated, to the oral antimicrobial agent used was required.

Adjunctive therapy: Adjunctive surgical therapy for the skin and skin structure infections was at the investigator's discretion; however, the name and date(s) of the procedure were to be recorded.

Schedule of assessments: The following chart (prepared by the applicant) summarizes the schedule of clinical and microbiological evaluations during the study trial, and the subsequent text reviews protocol recommendations for clinical, microbiologic and safety assessments during the study:

CLINICAL AND MICROBIOLOGIC ASSESSMENTS FOR PROTOCOL 89CE20-0449

Assessment	Pre-treatment	During Parenteral Therapy	Last Day of Parenteral Therapy	Last Day of Oral Therapy (if applicable)	10-14 Days Post-Therapy (Follow-up)
Medical History/ Physical Exam	X				
Signs and Symptoms	X	Daily	X	X	X
Clinical Response			X	X	X
Cultures of Infected Site	X	X[a]	X[b]	X[b]	X[b]
Blood Cultures	X	Repeat every 48 hours until negative			
Bacteriological Response			X	X	X
Clinical Laboratory Tests	X	X[c]	X	Repeat abnormal and related value until normal or return to baseline	

a - Every 3-5 days if material is available.
b - If material is available.
c - Every 3-5 days.

CLINICAL ASSESSMENTS:

Pretreatment evaluation: The initial evaluation was to be performed prior to start of therapy, and the infection was to be classified by the investigator into one or more of the following subgroups: superficial and bullous impetigo, folliculitis, furunculosis, and carbunculosis, hidradenitis, wound infections (surgical or traumatic), erysipelas, or cellulitis, including preseptal, buccal or cellulitis secondary to a viral exanthem (e.g., varicella).

Signs and symptoms: An assessment of signs and symptoms and measurement of body temperature were to be performed during the pretreatment evaluation, daily during study drug (parenteral) therapy, at the end of study drug therapy, at the end of oral therapy (if applicable), and at a follow-up visit after the end of all antimicrobial therapy. Each of the following signs and symptoms was to be rated by the investigator on a scale of absent, mild, moderate, or severe (0,1,2,3):

-- Pain
-- Redness or discoloration
-- Swelling
-- Drainage
-- Ulceration or tissue necrosis

Clinical response: See EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS Section to follow

MICROBIOLOGIC ASSESSMENTS:

Specimen Selection: Specimens for microbiologic evaluation were to be obtained from the infected site of each patient prior to initiation of antimicrobial therapy. If clinically indicated, follow-up specimens from the infected site were to be obtained every 3-5 days during therapy, at the end of study drug (parenteral) therapy, at the end of oral therapy (if applicable), and at the 10-14 day post-therapy evaluation.

Venous blood was to be obtained for culturing at the discretion of the individual investigator. If performed, pre-treatment blood cultures were to be obtained prior to the initiation of antimicrobial therapy, with one set of blood cultures to be obtained from each of two different, non-infected sites, with a several minute interval between each venipuncture; if the child's size precluded obtaining two sets of blood cultures, a single set would be accepted to suffice. If any pre-treatment blood culture yielded microbial growth, a set of follow-up cultures were to be obtained every 48 hours until they did not yield bacterial growth. Each follow-up series was to consist of two sets of blood cultures.

All patients 18 months or younger with facial (buccal) or periorbital cellulitis or evidence of sepsis or *H. influenzae* infection were required to have a lumbar puncture to rule out central nervous system infection

prior to randomization to study drug; moreover, patients of any age with evidence of bacterial infection of the central nervous system were not to be enrolled in the study or, if already enrolled, were to be immediately removed and treated with an appropriate antimicrobial.

Specimen processing: Aerobic cultures and a gram stain were to be performed on all specimens and, when indicated, anaerobic cultures were to be performed on all uncontaminated specimens obtained from normally sterile sites. Each probable pathogen was to be identified to the species level, and to be tested for antibiotic susceptibility and beta-lactamase production.

In Vitro Susceptibility Test Methods: All pathogens were to be tested for susceptibility to ampicillin, ampicillin/sulbactam (Unasyn), and cefuroxime either by disk diffusion method or by minimum inhibitory concentration (MIC) determination.

Medical Officer's Comment: Ampicillin/sulbactam susceptibility testing methods were established in NDA 50-608 and published in the approved package insert and in the National Committee for Clinical Laboratory Standards (NCCLS) documents. In the skin/skin structure study, pathogens were also tested for susceptibility to an oral transitional antibiotic when applicable.

The recommended broth or agar dilution methods of susceptibility testing were described in the approved package insert. Tubes were inoculated to contain 10^{-5} to 10^{-4} organisms/mL and plates were spotted with 10^{-4} organisms. Ampicillin/sulbactam was diluted using a fixed 2:1 concentration ratio and the minimum inhibitory concentration (MIC) was reported in terms of ampicillin in the presence of sulbactam at a constant 2 parts ampicillin to 1 part sulbactam. The MIC interpretive criteria for ampicillin/sulbactam used in these studies (and contained in the approved package insert) are presented in Table 2 below:

Table 2. MIC Interpretive Criteria for Ampicillin/Sulbactam*

Organisms	Susceptible	Moderately Susceptible	Resistant
Gram-negative enterics and staphylococci	≤8	16	≥32
Hemophilus	≤2	--	≥4
Enterococci†	--	≤8	≥16
Nonenterococcal streptococci and other gram-positives†	≤0.12	0.25-2	≥4

*Concentrations presented are in µg/ml of ampicillin.
†According to NCCLS recommendations, the interpretive criteria for ampicillin/sulbactam when testing enterococci, nonenterococcal streptococci and other gram-positives should be the same as those used for ampicillin.

For the disk diffusion method, the disk mass to be used for each antibiotic is as follows: ampicillin (10 mcg), ampicillin/sulbactam (10 mcg/10 mcg), and cefuroxime (30 mcg). The zone diameter interpretive criteria for ampicillin/sulbactam used in these studies are presented in Table 3 below:

Table 3. Zone Diameter Interpretive Criteria for Ampicillin/Sulbactam

Organisms	Susceptible	Moderately Susceptible	Resistant
Gram-negative enterics and staphylococci	≥17 mm	14-16 mm	≤13 mm
Hemophilus	≥20 mm	--	≤19 mm
Enterococci*	--	≥17 mm	≤16 mm
Nonenterococcal streptococci and other gram-positives*	≥30 mm	22-29 mm	≤22 mm

*According to NCCLS recommendations, the interpretive criteria for ampicillin/sulbactam when testing enterococci, nonenterococal streptococci and other gram-positives should be the same as those used for ampicillin.

For testing ampicillin/sulbactam against gram-negative enterics and staphylococci the zone diameter interpretive standards recommended by the NCCLS are different than those in the approved package insert. The NCCLS standards (as listed above) in Document M2-A4 are: ≤13 mm, resistant; 14-16 mm, intermediate; and ≥ 17 mm, susceptible; while product label criteria are ≤ 11 mm, resistant; 12-13 mm, intermediate; and ≥ 14 mm, susceptible. To insure standardization across all sites, the NCCLS disk diffusion criteria, rather than those in the product label, were used to analyze the U.S. microbiologic data in the present NDA supplement. NCCLS standards are more conservative than those in the product label.

In the present NDA supplement, anaerobic susceptibility testing was conducted using agar/broth dilution methods or the disk elution test. The recommended procedures for both methods were referenced in the NCCLS document M11-T2. MIC breakpoints for ampicillin/sulbactam were: ≤ 8 mcg/mL, susceptible; 16 mcg/mL, moderately susceptible; and ≥ 32 mcg/mL, resistant.

Susceptibility testing methods and interpretive criteria for the other antimicrobials used in these studies were those recommended by the NCCLS in Documents M2-A4.

Beta-lactamase Test: All presumptive pathogens were to be tested for constitutive beta-lactamase production using a rapid chromogenic cephalosporin (e.g., nitrocefin) test if the organism's ability to produce beta-lactamase could not be predicted from a species identification. Thus, gram-negative bacilli were to be routinely tested, but pathogens in the genus *Streptococcus* would not. (*Enterococcus* spp., if a presumptive pathogen, would be tested.)

SAFETY ASSESSMENTS:

Adverse Events: All volunteered or observed adverse experiences were to be recorded on the Case Report Form (CRF), specifying the time of onset, duration, severity, outcome, and relationship to study medication.

Laboratory Evaluation: Clinical laboratory tests were to be performed in each patient prior to initiation of therapy, every 3-5 days during the course of therapy, and on the last day of study drug (parenteral) therapy. For any test result which was abnormal at the end of study drug therapy, repeat testing of the abnormal and related tests was to be performed until the abnormality returned to within the normal range or to the baseline value.

The clinical laboratory tests to be performed were the following: Complete blood count (including platelet count and differential) and blood chemistries including creatinine, total bilirubin, SGOT, SGPT, BUN, and electrolytes (chloride, sodium, and potassium).

B. EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS

APPLICANT-DEFINED EVALUABILITY CRITERIA

According to the applicant, the evaluation of the efficacy of Unasyn in treating pediatric patients with SSTI was based on the investigator's evaluation of a patient's clinical and bacteriological response at the end of parenteral therapy, end of oral follow-up therapy, and 10 to 14 days post therapy. The criteria for efficacy evaluability were as follows:

1. Met protocol inclusion/exclusion criteria.

2. Received sufficient exposure to study drug therapy. Sufficient exposure was defined as $\geq$ 8 doses for patients in the Unasyn group and $\geq$6 doses for patients in the cefuroxime treatment group treated with a dosing regimen of every 8 hours and $\geq$ 8 doses for patients in the cefuroxime group treated with a dosing regimen of every 6 hours.

3. Had an appropriate pretreatment culture specimen of the infected site under study and/or a pretreatment blood culture which yielded at least one pathogen thought to be the causative agent of the infection. The pathogen isolated from the pretreatment cultures also needed to be susceptible to the assigned study (parenteral) drug.

4. Received no other parenteral antimicrobial therapy in the 48 hours before the start of treatment with study (parenteral) drug. Use of oral antimicrobial agents during this period were allowed.

5. Received no other antibiotics during treatment with study (parenteral) drug.

APPLICANT-DEFINED CLINICAL EFFICACY OUTCOMES

According to the applicant, the investigator performed an evaluation of the clinical efficacy of the drug therapy at the end of the course of study drug (parenteral) therapy, at the end of the course of oral therapy (if applicable), and 10-14 days after the end of all antimicrobial therapy. The terms used to classify clinical response were different for the different times of evaluation.

END OF STUDY DRUG THERAPY

Clinical Cure: This designation required that all of the following criteria were met:

1. The patient was afebrile for at least 24 hours and other systemic signs and symptoms either had resolved or were resolving satisfactorily.

2. The infected site appeared satisfactory, i.e, normal healing was occurring or had occurred.

3. Relevant clinical laboratory tests were within either normal or expected limits.

4. No additional antimicrobial therapy was required.
   Medical Officer's Comments: An assessment of clinical cure could not be selected at the end of study drug therapy if the patient received additional therapy with oral antimicrobials.

Clinical Improvement: This designation required that the clinical response was sufficient to discharge the patient but did not meet all the criteria necessary for "clinical cure".

Clinical Failure: The response to the study drug was inadequate, and the patient required alternative non-study therapy.

Not Evaluable: Determination of clinical efficacy was not possible.

END OF ORAL TRANSITIONAL THERAPY (IF APPLICABLE)

Clinical Cure: This designation required that complete healing had occurred, and no additional antimicrobial therapy was needed.

Clinical Failure: Recurrence of signs and symptoms of infection had occurred, and additional antimicrobial therapy was required.

Not Evaluable: The determination of clinical efficacy was not possible.

FOLLOW-UP AT END OF ALL THERAPY (10-14 DAYS POST-THERAPY)

Clinical Cure: This designation required that complete healing had occurred, and no additional antimicrobial therapy was needed.

Clinical Failure: Recurrence of signs and symptoms of infection had occurred, and additional antimicrobial therapy was required.

Not Evaluable: The determination of clinical efficacy was not possible.

APPLICANT-DEFINED MICROBIOLOGIC EFFICACY OUTCOMES

According to the applicant, the investigator also performed an evaluation of the bacteriologic efficacy of the drug therapy at the end of the course of study drug (parenteral) therapy, at the end of the course of oral therapy (if applicable), and 10-14 days after the end of all antimicrobial therapy. The following three classifications of bacterial outcome were used for evaluations at each of the three evaluations periods:

Eradication: Elimination of probable pathogen(s) as determined by repeat culture or absence of appropriate material for follow-up culture. All patient cultures, including blood cultures, must be negative.

Failure: Persistence of probable pathogen(s) at the infected site after therapy. This may include partial elimination of multiple pathogens or the appearance of a new pathogen(s) at the infected site.

Indeterminate: Bacteriologic outcome which could not be determined or classified as eradication or failure.

Medical Officer's Comments: The medical officer used different criteria from the applicant to determine evaluability. In consideration of the known difficulties in obtaining adequate microbiologic specimens for SSTI, the Division of Anti-Infective Drug Products (DAIDP), in the "Points to Consider" (PTC) document allows for the definition of a clinically evaluable subpopulation as well as a clinically and microbiologically evaluable subpopulation in trials designed to demonstrate the safety and efficacy of drugs for SSTI.

In the review of this indication, the medical officer, therefore, has adopted an approach which allows separate assessments of a patient's clinical and microbiologic evaluability. This approach allowed the medical officer to capture important clinical data from patients who were excluded by the applicant for problems with the microbiologic diagnosis (such as the failure to perform appropriate cultures at appropriate times). It should be noted that the applicant developed the SSTI protocol at a time before publication of the PTC document, when bacteriologic confirmation of SSTI was still being requested by the FDA.

Thus, as outlined in the PTC document, the medical officer defined two evaluable populations. One population was considered clinically evaluable only. Clinically evaluable patients included all patients who met clinical evaluability criteria without regard to bacteriologic evaluation. The second evaluable patient population was defined as both clinically and microbiologically evaluable, which will be referred to as the "fully evaluable" patient population in this document. Fully evaluable patients included all patients who met full evaluability criteria, which included required microbiologic data.

MEDICAL OFFICER-DEFINED EVALUABILITY CRITERIA

The following criteria were used by the medical officer to define a CLINICALLY EVALUABLE patient:

1. **Patient was between the ages of 3 months and sixteen years of age.**

2. A SSTI was diagnosed clinically by the presence of at least two of the following signs and/or symptoms associated with SSTI: redness, swelling, drainage, ulceration, pain, or the presence of fever >38°C. If the findings of lymphadenopathy or lymphangitis were observed and recorded by the investigator, these signs were included as one of the two required specific signs and symptoms of SSTI.

3. A clinical assessment was performed at admission to the study, at the end of study drug therapy, and no less than 5 days post-antimicrobial therapy. If the investigator had opted to treat with a transitional course of oral therapy, the patient was required to have a clinical assessment at the end of parenteral study drug therapy, and a second at no less than 5 days after completion of all antimicrobial therapy.

   Note: Although the applicant considered patients who completed 48 hours of study drug evaluable at time of discontinuation of parenteral therapy, the medical officer believes that some time period must elapse between the cessation of antimicrobial therapy and the assessment of study drug efficacy. Both time allotted for drug to be eliminated from the patient's system, and time allotted for the redevelopment of signs and symptoms of infection in patients whose bacterial population was suppressed but not eradicated by the study therapy should be included in this period. Therefore, the medical officer considered patients whose post-treatment assessments were performed prior to 5 days after the completion of all antimicrobial therapy to be not evaluable. It is presently DAIDP policy to require a follow-up assessment after the discontinuation of all study drugs.

4. A minimum of two full days of therapy (8 doses of Unasyn or 6 to 8 doses of cefuroxime) was required to be considered clinical failures or successes.

5. The IDSA Guidances for the evaluation of anti-infective drug products recommend that patients be considered evaluable if they have received $\leq$ 24 hours of treatment with a presumably effective oral anti-infective drug within 48 hours prior to receipt of study drug for an infectious process which requires a standard duration of therapy of $\geq$ 7 days.

   Therefore, the medical officer considered any patient who had received >24 hours of treatment with oral antimicrobial therapy within 48 hours prior to receipt of study drug as not evaluable. Additionally, any patient who had received parenteral antimicrobials within 48 hours prior to enrollment was considered not evaluable by the medical officer.

6. Patients receiving concurrent anti-infective therapy were considered to be not evaluable.

7. Adjunctive therapy for the skin and skin structure infections was to be performed at the investigator's discretion; however, the name and date(s) of the procedure were to be recorded in the CRF. The medical officer considered surgical procedures performed within 48 hours of first receipt of study drug as adjunctive therapy; surgical incision and drainage or wound drainage after 48 hours of antimicrobial therapy was considered a failure of the study drug

to contain the infection.

8. It is common clinical practice in pediatrics, when treating skin and skin structure infections, to provide a portion of the antimicrobial therapy via the parenteral route, and then transition to an oral antimicrobial agent to complete therapy. The present protocol allowed such transitional (oral) therapy, but is vague as to protocol restrictions regarding duration of transitional oral therapy. The protocol does state that the duration of administration of parenteral drug was not to exceed 14 days. Since it would be very uncommon in clinical practice to treat a skin and skin structure infection for longer than two to three weeks, the medical officer found it reasonable to also limit the duration of transitional (oral) therapy to a period not to exceed 14 days. Thus, patients receiving greater than 14 days of transitional (oral) therapy, following parenteral drug therapy, were considered not evaluable by the medical officer.

   Note: As the labeling will need to address the use of transitional (oral) therapy following parenteral Unasyn administration for this indication, the medical officer finds that establishing such evaluability criteria will aid in providing clear, specific and clinically relevant guidance on the use of transitional therapy following parenteral Unasyn administration.

The following criteria were used by the medical officer to define a FULLY (clinically and bacteriologically) EVALUABLE patient:

1. A fully evaluable patient must meet all the above mentioned criteria for clinical evaluability.

2. A pre-treatment culture was performed by appropriate technique within 24 hours of enrollment.

3. A pathogenic bacteria was recovered from a baseline clinical culture. In the majority of cases, the recovery of coagulase-negative staphylococci, micrococci, *Corynebacterium* species and diptheroids represent the normal flora of the skin. Therefore, for the most part, the medical officer considered patients in whom only these organisms were recovered to be not evaluable for microbiologic purposes.

   Exception to this criterion was made for patients with oropharyngeal infections or bite wounds; in such cases, these microbiologic flora were considered to represent potential true pathogens.

4. Susceptibility testing was performed for both study drugs. The pathogen must be susceptible to the assigned treatment regimen.

5. A post-treatment culture was performed greater than 5 days post-therapy, or, "no source to culture" was documented by the investigator.

   Note: As the labeling for ampicillin/sulbactam specifically claims efficacy in the eradication and treatment of infections caused by ampicillin-resistant, ampicillin/sulbactam susceptible, beta-lactamase

positive organisms, the medical officer also evaluated a subset of the fully evaluable patients whose baseline pathogens demonstrated ampicillin-resistance, ampicillin/sulbactam susceptibility and beta-lactamase production. This subset of the fully evaluable patient population with ampicillin-resistant, beta-lactamase producing baseline pathogens will be referred to as CRITICAL PATHOGEN EVALUABLE patients during efficacy analyses.

In summary, the following criteria were used by the medical officer to define a CRITICAL PATHOGEN EVALUABLE PATIENT:

1. *A critical pathogen evaluable patient must meet all the criteria for a fully evaluable patient.*

2. *The pathogenic bacteria recovered from the baseline clinical culture must be demonstrated to be ampicillin-resistant, ampicillin/sulbactam susceptible and beta-lactamase positive.*

MEDICAL OFFICER-DEFINED CLINICAL EFFICACY OUTCOMES

The medical officer also used different terms and criteria for determining efficacy outcomes. According to the medical officer, evaluable patients could be assigned a clinical outcome indicating failure at any time after receiving 48 hours of the study drugs. The clinical outcome of success could only be assigned at the post-therapy evaluation. The medical officer used the following response categories to describe clinical failure at any time during study therapy and clinical success at the post-therapy evaluation:

Failure: The persistence of major signs or symptoms of SSTI requiring removal from study drug therapy, or the administration of additional or alternative therapy, including surgical intervention, or the development of any new signs or symptoms of SSTI.

Note: The response of failure could be assigned after 48 hours on therapy if the patient was removed from the study for the persistence or worsening of symptoms, or was treated with alternative or additional therapy.

Success: The complete resolution of all major signs and symptoms used to initially document the infection. No new signs or symptoms of infection could have developed either during or after treatment.

MEDICAL OFFICER-DEFINED MICROBIOLOGIC EFFICACY OUTCOMES

According to the medical officer, evaluable patients could be assigned a microbiologic outcome indicating failure at any time after receiving 48 hours of the study drugs. The microbiologic outcome of eradication could only be assigned at the post-therapy evaluation. The medical officer used the following categories to describe the microbiologic outcome:

Failure:

A.) *Documented Persistence:* The causative organism was recovered from a post-treatment culture or the organism was

recovered from a during treatment culture and the patient was placed on alternative antimicrobial therapy.

B.) *Presumptive Persistence:* The patient had continued signs and/or symptoms of SSTI at the post-treatment evaluation but no organisms could be recovered from culture; or the patient was placed on alternative antimicrobial therapy at any time after the first 48 hours of study drug therapy for the persistence or worsening of signs and/or symptoms and no organism was recovered from culture or a culture was not performed.

C.) *Superinfection:* A new organism was recovered from a post-treatment culture and signs and/or symptoms of SSTI continued to be present in the patient; or a new organism was recovered from a during-therapy culture and the patient was started on an alternative antimicrobial therapy.

Eradication: At the post-treatment assessment, the causative organism was not recovered from a culture of the involved area; or sufficient clinical resolution had occurred such that there was no material/site available for culture.

NOTE: To be considered a "fully evaluable success", the patient must have clinical success and bacteriologic eradication, or presumptive eradication. If the patient developed superinfection, even during oral antibiotic therapy, they were considered a clinical and bacteriologic failure.

C. STUDY DESIGN, PATIENT EVALUATION, AND EFFICACY ANALYSES

Study Design and Evaluability

The applicant conducted this study protocol with patients enrolled by investigators at 13 centers in the United States (note: one center enrolled no patients for this protocol). Overall, 234 patients were enrolled.

The following table summarizes the number of patients in the intent to treat and evaluable and nonevaluable patient populations as rendered by the applicant and by the medical officer for each treatment regimen:

INTENT TO TREAT (ITT) AND EVALUABLE AND NONEVALUABLE PATIENTS (PER APPLICANT AND MEDICAL OFFICER [MO]) BY TREATMENT REGIMEN

	Unasyn	Cefuroxime
No. Patients Enrolled (Intent to Treat Population [ITT])	154	80
No. of Evaluable Patients per Applicant	59	39
No. of Nonevaluable Patients per Applicant	95	41
No. of Clinically Evaluable' Patients per MO*	60	39
No. of Fully Evaluable Patients per MO	(28)	(24)
No. of Nonevaluable Patients per MO	94	41

' includes clinically evaluable and fully evaluable patients
* MO=Medical Officer

Medical Officer's Comments: As outlined previously, the medical officer's criteria for evaluability differed from the applicant's criteria. Specifically, the medical officer's criteria for evaluability differed in 4 areas: 1) A clinically evaluable population was defined wherein patients without baseline pathogens isolated in culture would be considered evaluable. 2) Those patients who did not have follow-up evaluation at least 5 days after all antimicrobial therapy was discontinued were considered not evaluable. 3) Patients who received oral antimicrobials for greater than 24 hours within 48 hours of study drug administration were considered not evaluable. 4) Patients who received greater than 14 days of oral transitional therapy following the administration of parenteral study drug therapy were considered not evaluable. These differences in evaluability criteria led to differences in categorizing patients as evaluable and not evaluable. Appendix A lists by patient number and treatment regimen each patient whose evaluability or outcome status differed between medical officer and applicant, with a corresponding reason for the applicant's and medical officer's determination. Additionally, the next tables summarize and compare the applicant's and medical officer's reasons for excluding patients from the efficacy analysis:

SUMMARY OF APPLICANT REASONS FOR EXCLUSION FROM EFFICACY ANALYSIS (i.e., nonevaluable patients)

REASON	UNASYN	CEFUROXIME
No baseline pathogen (NBP)	80	33
Prior parenteral antibiotic (abx)	2	0
Less than minimum therapy	9	6
Inappropriate diagnosis	3	1
Inappropriate dose	0	1
No susceptibility data	1	0
TOTAL	95	41

SUMMARY OF MEDICAL OFFICER REASONS FOR EXCLUSION FROM EFFICACY ANALYSIS (i.e., nonevaluable patients)

REASON	UNASYN	CEFUROXIME
Inadequate follow-up (no F/U) post-therapy (i.e., <5 days)	47	24
Prior Antibiotics (abx)		
(>24 hours oral)	25	8
(parenteral)	4	0
Less than minimum therapy	8	6
Inappropriate diagnosis[1]	5	0
Concurrent antibiotics	2	1
Retained foreign body	0	1
Received >14 days transition therapy	3	1
TOTAL	94	41

[1] Inappropriate diagnoses included CSF pleocytosis, prepatellar bursitis, endophthalmitis, and mastoiditis (2).

Patient Enrollment by Investigation Site

The following table presents the number of patients in the intent to treat (ITT) and evaluable patient populations (as rendered by the medical officer and by the applicant) by investigation site:

INTENT TO TREAT (ITT) AND EVALUABLE PATIENTS BY INVESTIGATION SITE

		ITT (Patients Enrolled)			MO Evaluable[1]			Applicant Evaluable		
Investigator	Site	T[2]	U[3]	C[4]	T	U	C	T	U	C
Azimi	Oakland,CA	104	69	35	22	12	10	42	21	21
Baker	Houston, TX	4	2	2	3	1	2	1	0	1
Dajani	Detroit, MI	16	11	5	9	6	3	7	5	2
Kim	Los Angeles, CA	19	12	7	11	5	6	6	3	3
Barson	Columbus, OH	32	20	12	20	11	9	15	9	6
Stephan	Cincinnati, OH	10	7	3	7	5	2	4	3	1
Stechenberg	Springfield, MA	2	2	0	2	2	0	1	1	0
Congeni	Akron, OH	5	3	2	2	2	0	3	2	1
Karasic	Pittsburgh, PA	0	0	0	0	0	0	0	0	0
Long	Philadelphia, PA	30	20	10	16	12	4	16	14	2
Aronoff	Morganstown, WV	4	2	2	1	0	1	2	1	1
Schutze	Little Rock, Arkansas	3	1	2	2	0	2	1	0	1
Harrison	Omaha, NE	5	5	0	4	4	0	0	0	0
TOTAL		234	154	80	99	60	39	98	59	39

[1]MO Evaluable=Medical Officer Evaluable (includes both clinically and fully evaluable patients)
[2]T=Total
[3]U=Unasyn
[4]C=Cefuroxime

Medical Officer's Comments: Although one center (Oakland, CA) enrolled a substantial proportion of the total patients (44%), no center enrolled greater than 50% of the ITT or evaluable patient populations.

Demographics of Intent to Treat and Evaluable Patients

Medical Officer's comments: Throughout the remainder of this review of protocol SSS 89C320-0449, evaluable patients will refer to the subset of patients as defined by the medical officer.

The following table compares the demographics of the ITT and the clinically and fully evaluable patients as rendered by the medical officer:

PATIENT DEMOGRAPHICS FOR THE INTENT TO TREAT AND MEDICAL OFFICER EVALUABLE (CLINICALLY AND FULLY EVALUABLE) POPULATIONS

Characteristic	Intent To Treat		Clinically Evaluable		Fully Evaluable	
	U[1] N (%)	C[2] N (%)	U N (%)	C N (%)	U N (%)	C N (%)
Total Patients	154	80	60	39	28	24
Sex						
Male	90 (58)	40 (50)	35 (58)	16 (41)	11 (39)	10 (42)
Female	64 (42)	40 (50)	25 (42)	23 (59)	17 (61)	14 (58)
Age (months)						
mean	51.6	56.4	52.2	54.3	53.4	52.2
range						
median			36.5	58.0	37.5	60.5
mode			19.0	8.0	22.0	16.0
Race						
White	50 (33)	25 (31)	30 (50)	15 (39)	6 (21)	9 (37)
Black	53 (34)	27 (34)	19 (32)	11 (28)	13 (47)	6 (25)
Hispanic			6 (10)	9 (23)	4 (14)	5 (21)
Other	51 (33)	28 (35)	5 (8)	4 (10)	5 (18)	4 (17)
Weight (kgs)						
Male						
mean	18.9	20.2	19.1	21.5	17.4	23.0
range						
Female						
mean	19.5	17.6	19.4	16.3	21.9	15.0
range						

[1] U=Unasyn
[2] C=Cefuroxime

Medical Officer's Comments: The demographic characteristics of the ITT and clinically and fully evaluable patients for both the Unasyn and cefuroxime study drug treatment arms appear similar in gender distribution, age, race and weight by gender. However, there is a trend toward increased age for patients treated with cefuroxime in

both the ITT and clinically evaluable patients. There is also a trend toward increased weight for male patients assigned to the cefuroxime treatment arm, and toward increased weight for females assigned to the Unasyn treatment arm for all populations.

Evaluable Patients

Treatment Characteristics

The following table compares treatment characteristics between evaluable patients receiving Unasyn and evaluable patients receiving cefuroxime:

TREATMENT CHARACTERISTICS OF EVALUABLE PATIENTS BY TREATMENT REGIMEN

Characteristic	Clinically Evaluable		Fully Evaluable	
	Unasyn N (%)	Cefuroxime N (%)	Unasyn N (%)	Cefuroxime N (%)
Study drug unit dose (mg/kg)				
mean	70.3	44.6	70.0	45.1
range				
median	74.0	49.2	73.4	49.7
mode	75.0	50.0	75.0	50.0
Study drug duration (days)				
mean	4.5	4.7	4.6	5.1
range				
median	4.0	4.0	4.0	4.0
mode	4.0	4.0	4.0	4.0
Transition (oral) therapy				
yes	57 (95)	36 (92)	27 (96)	22 (92)
no	3 (5)	3 (8)	1 (4)	2 (8)
Oral therapy duration (days)				
mean	8.5	8.2	8.5	7.7
range				
median	8.0	8.0	8.0	7.0
mode	7.0	7.0	7.0	7.0
Surgical procedure				
yes	10 (17)	7 (18)	5 (18)	6 (25)
no	50 (83)	32 (82)	23 (82)	18 (75)
TOTAL PATIENTS	60	39	28	24

Medical Officer's Comments: The average unit dose of ampicillin/sulbactam administered in the clinically and fully evaluable populations was similar; 70.3 and 70.0 mg/kg/dose, respectively. Since ampicillin/sulbactam was generally administered four times daily, and the median dose of ampicillin/sulbactam administered to the clinically and fully evaluable patients was 74.0 and 73.4, respectively, the majority of patients in the Unasyn

treatment regimen received a daily dose of ampicillin/sulbactam greater than or equal to 292 mg/kg/day. The average unit dose of cefuroxime administered was also similar in the clinically and fully evaluable populations; 44.6 and 45.1 mg/kg/dose, respectively. Since cefuroxime was generally administered three times daily, and the median dose of cefuroxime administered to the clinically and fully evaluable patients was 49.2 and 49.7, respectively, the majority of patients in the cefuroxime treatment regimen received a daily dose of cefuroxime greater than or equal to 147 mg/kg/day. The mean and median dosages of cefuroxime are higher than the protocol dosage recommendation of 50-100 mg/kg/day, but less than the pediatric dosage recommendations for bone and joint infections and meningitis (150 mg/kg/day and 200 mg/kg/day, respectively). The study drug duration was similar between evaluable patients in the Unasyn and cefuroxime treatment arms.

Additionally, a similar number of Unasyn-treated and cefuroxime-treated patients received oral transition therapy, and the two groups had similar durations of oral therapy. In the clinically evaluable patients, the average duration of oral therapy was 8.5 and 8.2 days for Unasyn- and cefuroxime-treated patients, respectively; in the fully evaluable patients, the average duration of oral therapy was 8.5 and 7.7 days for Unasyn- and cefuroxime-treated patients, respectively. Oral agents used in the two groups were similar and included Augmentin, cephalexin, amoxicillin, penicillin, Ceclor, and dicloxicillin. When the medical officer reviewed the clinical course of all evaluable patients to determine what percentage of patients met the transition criteria for oral therapy outlined in the applicant's protocol, a large percentage of patients from both treatment regimens met the transition criteria. Of fifty-seven patients receiving oral therapy in the clinically evaluable Unasyn-treated group, 55 (96%) met the transition requirement prior to initiation of oral therapy; twenty-seven of 27 fully evaluable Unasyn-treated patients (100%) fulfilled transition criteria. A similarly large percentage of the cefuroxime-treated patients also met the oral therapy transition requirements; thirty-three of 36 clinically evaluable cefuroxime-treated patients (92%) fulfilled the transition criteria, and 22 of 22 fully evaluable patients (100%) fulfilled the transition requirements.

The clinically and fully evaluable patient populations of the Unasyn- and cefuroxime-treated patients were also similar in the percentage of patients who underwent surgical procedures during the study period.

Note: Since the majority of evaluable patients were treated with transition (oral) therapy after discontinuation of parenteral drug therapy, the medical officer finds that this aspect of the clinical trial should be adequately related in the labeling of Unasyn for pediatric usage. Further, consideration should be given to providing the clinician with some information and guidance regarding the criteria for transition to oral therapy.

Primary Diagnoses of Infection

The following table compares the primary diagnoses of infection between evaluable patients treated with Unasyn and evaluable patients treated with cefuroxime:

PRIMARY DIAGNOSIS OF INFECTION FOR MEDICAL OFFICER EVALUABLE PATIENTS BY TREATMENT REGIMEN

Characteristic	Clinically Evaluable		Fully Evaluable	
	Unasyn N (%)	Cefuroxime N (%)	Unasyn N (%)	Cefuroxime N (%)
Primary Diagnosis Folliculitis/ Furunculosis/ Hidradenitis	3 (5)	1 (2.7)	2 (7)	0
Impetigo	3 (5)	0	3 (11)	0
Cellulitis/ Lymphadenitis/ Erysipelas	26 (43)	20 (51)	11 (39)	12 (50)
Wound Infection	16 (27)	16 (41)	9 (32)	11 (46)
Adenitis	2 (3)	1 (2.7)	1 (4)	0
Facial/Preseptal Cellulitis	10 (17)	1 (2.7)	2 (7)	1 (4)
TOTAL PATIENTS	60	39	28	24

Medical Officer's Comments: Overall, the distribution of evaluable patients by primary diagnosis is similar for the two treatment regimens, with the majority of both Unasyn- and cefuroxime-treated patients diagnosed with cellulitis/lymphadenitis/erysipelas or wound infection. Of note, is the increased number of patients with facial or preseptal cellulitis in the Unasyn-treated patients of the clinically evaluable patient population (10/60 [17%] vs. 1/39 [3%], p=0.05).

Efficacy Analyses

CLINICAL EFFICACY RESULTS

Overall Clinical Outcome

The following table summarizes the clinical outcome as rendered by the medical officer for the clinically, fully, and critical pathogen evaluable patient populations by treatment regimen:

CLINICAL OUTCOME FOR MEDICAL OFFICER EVALUABLE PATIENTS BY TREATMENT REGIMEN

Population	Unasyn				Cefuroxime			
	Total	S[1]	F[2]	%S[3]	Total	S	F	%S
Clinically Evaluable Patients	60	51	9	85.0	39	34	5	87.2
Fully Evaluable Patients	28	26	2	92.8	24	22	2	91.7
Critical Pathogen Evaluable Patients	16	15	1	93.8	10	8	2	80.0

[1] S=Success
[2] F=Failure.
[3] %S=Percent Successful Clinical Outcome

Medical Officer's Comments: Of the 60 clinically evaluable Unasyn-treated patients, 51 (85.0%) were considered clinical successes, and 9 (15.0%) were considered clinical failures. Of the 39 clinically evaluable cefuroxime-treated patients, 34 (87.2%) were considered clinical successes and 5 (12.8%) were considered clinical failures.

Examination of the subpopulation of fully evaluable patients reveals that of the 28 fully evaluable Unasyn-treated patients, 26 (92.8%) were considered clinical successes and 2 (7.2%) were considered failures. Of the 24 fully evaluable cefuroxime-treated patients, 22 (91.7%) were considered clinical successes, and 2 (8.3%) were considered failures. For critical pathogen evaluable patients, a subset of the fully evaluable patient population, fifteen of sixteen (93.8%) patients were considered clinical successes in the Unasyn-treated group, and 8/10 (80%) of cefuroxime-treated patients were considered clinical successes.

The 95% confidence intervals around the true difference in the overall clinical success rates are as follows:

CLINICAL SUCCESS
MO Clinically Evaluable: [-0.18, 0.14]
MO Fully Evaluable: [-0.17, 0.20]
MO Critical Pathogen Evaluable: [-0.22, 0.49]

Note: Using the DAIDP "two-tailed 95% confidence interval around the difference in outcomes" data analysis approach, the clinically evaluable population confidence interval should cross zero and remain within a lower bound delta of -0.15 to establish equivalence. For the fully evaluable population, the confidence interval should cross zero and remain within a lower bound delta of -0.10 to establish equivalence. For critical pathogen evaluable patients, the confidence interval should cross zero and remain within a lower bound delta of -0.10. Although the clinical outcomes for Unasyn- and cefuroxime-treated patients appear similar, because of the small numbers of evaluable patients available for efficacy analysis in this clinical trial, Unasyn does not fulfill the regulatory definition of therapeutic equivalence.

Clinical Outcome by Primary Diagnosis

The following tables report clinical outcome by primary diagnosis and treatment regimen for the evaluable patient populations:

CLINICAL OUTCOME BY PRIMARY DIAGNOSIS AND TREATMENT REGIMEN
CLINICALLY EVALUABLE PATIENTS

Primary Diagnosis	Unasyn				Cefuroxime			
	N[1]	S[2]	F[3]	%S[4]	N	S	F	%S
Folliculitis/ Furunculosis/ Hidradenitis	3	2	1	66.7	1	1	0	100
Impetigo	3	3	0	100	0	0	0	--
Cellulitis/ Lymphadenitis/ Erysipelas	26	23	3	88.5	20	17	3	85.0
Wound Infection	16	15	1	93.7	16	16	0	100
Adenitis	2	0	2	0	1	0	1	0
Facial/Preseptal Cellulitis	10	8	2	80	1	0	1	0
TOTAL PATIENTS	60	51	9	85.0	39	34	5	87.2

[1]N=Number
[2]F=Failure
[3]S=Success
[4]%S=Percent Successful Clinical Outcome

CLINICAL OUTCOME BY PRIMARY DIAGNOSIS AND TREATMENT REGIMEN
FULLY EVALUABLE PATIENTS

Primary Diagnosis	Unasyn				Cefuroxime			
	N[1]	S[2]	F[3]	%S[4]	N	S	F	%S
Folliculitis/ Furunculosis/ Hidradenitis	2	2	0	100	0	0	0	--
Impetigo	3	3	0	100	0	0	0	--
Cellulitis/ Lymphadenitis/ Erysipelas	11	10	1	90.9	12	11	1	91.6
Wound Infection	9	9	0	100	11	11	0	100
Adenitis	1	0	1	0	0	0	0	--
Facial/Preseptal Cellulitis	2	2	0	100	1	0	1	0
TOTAL PATIENTS	28	26	2	92.8	24	22	2	91.7

[1]N=Number
[2]F=Failure
[3]S=Success
[4]%S=Percent Successful Clinical Outcome

CLINICAL OUTCOME BY PRIMARY DIAGNOSIS AND TREATMENT REGIMEN
CRITICAL PATHOGEN EVALUABLE PATIENTS

Primary Diagnosis	Unasyn				Cefuroxime			
	N[1]	S[2]	F[3]	%S[4]	N	S	F	%S
Folliculitis/ Furunculosis/ Hidradenitis	2	2	0	100	0	0	0	--
Impetigo	2	2	0	100	0	0	0	--
Cellulitis/ Lymphadenitis/ Erysipelas	6	5	1	83.3	6	5	1	83.3
Wound Infection	6	6	0	100	3	3	0	100
Adenitis	0	0	0	--	0	0	0	--
Facial/Preseptal Cellulitis	0	0	0	--	1	0	1	0
TOTAL PATIENTS	16	15	1	93.8	10	8	2	80.0

[1]N=Number
[2]F=Failure
[3]S=Success
[4]%S=Percent Successful Clinical Outcome

Medical Officer's Comments: In the clinically evaluable patient population, the overall clinical success rate was 85.0% for Unasyn-treated patients, and 87.2% for cefuroxime-treated patients; the majority of patients in both treatment groups had a primary diagnosis of cellulitis/lymphadenitis/erysipelas or wound infection, although as previously noted, the Unasyn-treated patients population had a larger number of patients with a primary diagnosis of facial/preseptal cellulitis. The clinical success rates for patients with a primary diagnosis of cellulitis/lymphadenitis/erysipelas and wound infection are similar for both Unasyn-and cefuroxime-treated patients. In the fully evaluable patient population, the overall clinical success rate was 92.8% for Unasyn-treated patients, and 91.7% for cefuroxime-treated patients. The majority of patients in the fully evaluable population also carried a primary diagnosis of cellulitis/lymphadenitis/erysipelas or wound infection; the clinical success rates for these two primary diagnoses are similar for both Unasyn- and cefuroxime-treated patients. In the critical pathogen evaluable population, the overall clinical success rate was 93.8% for Unasyn-treated patients, and 80% for cefuroxime-treated patients; the majority of patients had a primary diagnosis of cellulitis/lymphadenitis/erysipelas or wound infection, and the clinical success rates for these two diagnoses are similar for both Unasyn- and cefuroxime-treated patients.

Clinical Outcome by Study Drug Dosage and Duration and Transitional Therapy Duration

The following tables evaluate clinical outcome by study dosage and duration and transitional (oral) therapy duration for both clinically and fully evaluable patients by treatment regimen:

STUDY DRUG DOSAGE AND DURATION AND TRANSITIONAL THERAPY DURATION BY TREATMENT REGIMEN AND CLINICAL OUTCOME FCR CLINICALLY EVALUABLE PATIENTS

	Study Drug Regimen			
	Unasyn		Cefuroxime	
	S[1]	F[2]	S	F
	N=51	N=9	N=34	N=5
Study Drug Dosage (mg/kg/dose)				
mean	70.5	69.7	44.3	47.1
median	74.0	72.6	49.1	50.0
range				
Study Drug Duration (days)				
mean	4.2	5.8	4.7	5.4
median	4.0	6.0	4.0	4.0
range				
Transitional (oral) Therapy Duration	N=50	N=7	N=32	N=4
(days)				
mean	8.5	8.1	8.5	5.8
median	8.0	8.0	8.0	5.5
range				

[1]S=Clinical Success
[2]F=Clinical Failure

STUDY DRUG DOSAGE AND DURATION AND TRANSITIONAL THERAPY DURATION BY TREATMENT REGIMEN AND CLINICAL OUTCOME FOR FULLY EVALUABLE PATIENTS

	Study Drug Regimen			
	Unasyn		Cefuroxime	
	S[1]	F[2]	S	F
	N=26	N=2	N=22	N=2
Study Drug Dosage (mg/kg/dose)				
mean	69.8	73.9	44.7	50.2
median	73.4	73.9	49.5	50.2
range				
Study Drug Duration (days)				
mean	4.4	8.0	5.1	5.5
median	4.0	8.0	4.0	5.5
range				
Transitional (oral) Therapy Duration	N=25	N=2	N=20	N=2
(days)				
mean	8.5	8.5	7.9	5.5
median	8.0	8.5	7.0	5.5
range				

[1]S=Clinical Success
[2]F=Clinical Failure

Medical Officer's Comments: Because a dosage range for both study drugs was permitted in the protocol, the medical officer compared the average unit doses of study drug for both the Unasyn- and cefuroxime-treated evaluable patients by clinical outcome to ensure that clinical failures were not associated with a lower dosing of study drug as compared to

clinical successes. No significant difference in the average unit dose of study drug administered was found between clinical successes when compared to clinical failures for the evaluable patient populations of both Unasyn- and cefuroxime-treated patients. For both clinically and fully evaluable patients treated with the Unasyn regimen, intravenous antimicrobial therapy was demonstrated to be of longer duration in patients deemed to be clinical failures; this difference was less pronounced in cefuroxime-treated patients, and did not reach statistical significance. In the clinically evaluable patient population, patients receiving cefuroxime who were determined to be clinical failures received shorter durations of transitional (oral) therapy; although the same trend is evident in the fully evaluable patient population, it did not reach statistical significance.

MICROBIOLOGIC EFFICACY RESULTS
FULLY EVALUABLE PATIENTS

Pathogen Level Analysis

The following table summarizes the bacteriologic outcome for each isolated baseline pathogen per treatment regimen in the fully evaluable patients:

BACTERIOLOGIC OUTCOME OF PATHOGENS PER TREATMENT REGIMEN
FULLY EVALUABLE PATIENTS

	Unasyn			Cefuroxime		
Organism Classification	N	#Erad	%Erad	N	#Erad	%Erad
Gram positive aerobes						
*Staphylococcus aureus**	18	16	89	12	10	83.3
Streptococcus pneumoniae	1	1	100	-	-	--
Streptococcus pyogenes	7	7	100	11	9	81.8
Viridans group streptococcus	1	1	100	-	-	--
Corynebacterium spp.	-	-	--	1	1	100
Gram negative aerobes						
Enterobacter spp.	-	-	--	1	1	100
Gram negative rod	-	-	--	1	1	100
Hemophilus influenzae	1	1	100	-	-	--
Hemophilus parainfluenzae	1	1	100	-	-	--
Klebsiella spp.	1	1	100	1	1	100
Moraxella spp.	-	-	--	1	1	100
Gram negative facultative anaerobes						
Pasteurella multocida	1	1	100	3	3	100
Pasteurella spp.	-	-	--	3	3	100
TOTAL	31	29	93.5	34	30	88.2

N=Number
#Erad=Number Eradicated
%Erad=Percent Eradicated
*Organisms reported as *Staphylococcus* spp. (coagulase positive) and those reported as *Staphylococcus aureus* have been grouped together under *Staphylococcus aureus*.

Medical Officer's Comments: There were 31 baseline pathogens isolated from the SSTI of the 28 fully evaluable Unasyn-treated patients, and 29 (93.5%) of these pathogens were eradicated. The majority of these pathogens belonged to two species, *Staphylococcus aureus* and *Streptococcus pyogenes;* the eradication rate for *S. aureus* was 89%, and the eradication rate for *S. pyogenes* was 100%. Additionally, there were 34 baseline pathogens isolated from the SSTI of the 24 fully evaluable cefuroxime-treated patients, and 30 (88.2%) of these pathogens were eradicated. The majority of pathogens isolated from the cefuroxime group were *S. aureus* and *S. pyogenes*, with eradication rates of 83.3% and 81.8%, respectively. Of note, in the cefuroxime group was the isolation of 6 isolates of *Pasteurella* species, with a rate of eradication of 100%.

The 95% confidence intervals around the true difference in the overall bacteriologic eradication rates for the fully evaluable patients follows:

BACTERIOLOGIC ERADICATION
MO Fully Evaluable: [-0.12, 0.22]

Using the DAIDP "two-tailed approach", the fully evaluable population confidence interval should cross zero and remain within a lower bound delta of -0.10.

Patient Level Analysis

As previously stated, twenty-six of the twenty-eight fully evaluable patients (92.8%) who received Unasyn were defined as clinical successes. These 26 patients were also defined as bacteriologic eradications; conversely, the two clinical failures in the fully evaluable Unasyn-treated group were also bacteriologic failures. Each of the two Unasyn-treated patients who were designated clinical and bacteriologic failures had *Staphylococcus aureus* as baseline pathogens. In the fully evaluable cefuroxime-treated group, 22 of twenty-four evaluable patients (91.7%) were defined as both clinical successes and bacteriologic eradications. The two clinical failures in the cefuroxime-treated group were also associated with bacteriologic failures (both patients had 2 baseline pathogens present, *Staphylococcus aureus* and *Streptococcus pyogenes*).

Medical Officer's Comments: The 95% confidence interval around the difference in clinical and bacteriologic efficacy at the patient level follows:

CLINICAL SUCCESS AND BACTERIOLOGIC ERADICATION
MO Fully Evaluable: [-0.17, 0.20]

As previously discussed, this confidence interval does not meet the DAIDP requirements for demonstration of therapeutic equivalence.

CRITICAL PATHOGEN EVALUABLE PATIENTS
Ampicillin-Resistant, Beta-Lactamase-Positive Organisms

Pathogen Level Analysis

The following table summarizes the bacteriologic response for each isolated baseline pathogen per treatment regimen in the critical pathogen evaluable patients:

BACTERIOLOGIC OUTCOME OF PATHOGENS PER TREATMENT REGIMEN
CRITICAL PATHOGEN EVALUABLE PATIENTS

	Unasyn			Cefuroxime		
Organism	N	#Erad	%Erad	N	#Erad	%Erad
Staphylococcus aureus	16	15	93.8	10	8	80.0
Streptococcus pyogenes	1	1	100.0	4	2	50.0
TOTAL	17	16	94.1	14	10	71.4

N=Number
#Erad=Number Eradicated
%Erad=Percent Eradicated

Medical Officer's Comments: There were 31 pathogens isolated from the 26 critical pathogen evaluable patients; twenty-six of these pathogens were critical pathogens. The pathogens isolated from the critical pathogen evaluable patients belonged to two species, *Staphylococcus aureus* and *Streptococcus pyogenes*. The eradication rate for *S. aureus* was 93.8% for the Unasyn-treated group, and 80% for the cefuroxime treated group. For *Streptococcus pyogenes*, the bacterial eradication rate was 100% in the Unasyn-treated group, and 50% in the cefuroxime-treated group. It should be noted that these failures in eradication of *S. pyogenes* in the cefuroxime-treated group were both associated with polymicrobial infections with *Staphylococcus aureus*.

The 95% confidence interval around the true difference in the overall bacteriologic eradication rates for critical pathogen evaluable patients follows:

BACTERIOLOGIC ERADICATION
MO Critical Pathogen Evaluable: [-0.10, 0.55]

Using the DAIDP "two-tailed approach", the critical pathogen evaluable population confidence interval should cross zero and remain within a lower bound delta of -0.10. Thus, the analysis of overall pathogen eradication in the critical pathogen evaluable population meets the regulatory requirements to establish equivalence; these results should be considered, however, in the context of the small number of patients analyzed, and the associated wide range of confidence interval obtained. Further, if this trend for bacterial eradication was extrapolated, with 25 patients in each treatment regimen, the 95% confidence interval would be (0.03, 0.43), indicating a greater bacterial eradication rate in the Unasyn-treated patients compared with the cefuroxime-treated patients.

The following table summarizes the bacteriologic response for each critical pathogen per treatment regimen in the critical pathogen evaluable patients:

BACTERIOLOGIC OUTCOME OF CRITICAL PATHOGENS PER TREATMENT REGIMEN
IN CRITICAL PATHOGEN EVALUABLE PATIENTS

	Unasyn			Cefuroxime		
Organism Classification	N	#Erad	%Erad	N	#Erad	%Erad
Staphylococcus aureus	16	15	93.8	10	8	80.0

N=Number
#Erad=Number Eradicated
%Erad=Percent Eradicated

Medical Officer's Comments: There were 26 critical pathogens isolated from the 26 critical pathogen evaluable patients. All critical pathogens isolated were *S. aureus*. There were 16 critical baseline pathogens isolated from 16 critical pathogen evaluable patients treated with Unasyn. Fifteen of 16 (93.8%) critical pathogens (i.e., *S. aureus*) in the Unasyn group were eradicated. There were 10 critical pathogens isolated from 10 fully evaluable patients treated with cefuroxime. Eight of 10 (80.0%) critical pathogens (i.e., *S. aureus*) in the cefuroxime group were eradicated.

The 95% confidence interval around the true difference in the critical pathogen eradication rate follows:

CRITICAL PATHOGEN ERADICATION
MO Critical Pathogen Evaluable: [-0.22, 0.49]

Using the DAIDP "two-tailed 95% confidence interval approach", the critical pathogen evaluable population confidence interval should cross zero and remain within a lower bound delta of -0.10. Thus, this analysis does not establish the regulatory definition of equivalence.

Patient Level Analysis

Medical Officer's Comments: In the final analysis for a critical pathogen to be identified with skin and skin structure infections in the *Indications and Usage* section of the package insert, the critical pathogen must have been eradicated and the patient must have had a favorable outcome (clinical success). The eradication rate is calculated by the following equation:

$$\frac{\text{The number of critical pathogens of a given genus and species eradicated from critical pathogen evaluable patients who are clinical successes}}{\text{Total number of critical pathogens of the same genus and species from all critical pathogen evaluable patients (clinical successes + failures)}} \times 100$$

From the above table it is clear that the only pathogen studied in sufficient number in the SSTI protocol was *Staphylococcus aureus*.

Study drug: Unasyn

There were 16 critical *S. aureus* pathogens isolated from baseline cultures; fifteen *S. aureus* isolates were eradicated, and the patients initially harboring these organisms were deemed clinical successes. Thus, the successful eradication rate is 15/16 (93.8%) for critical *S. aureus* isolates.

Study drug: cefuroxime

There were 10 critical *S. aureus* pathogens isolated from baseline cultures; eight *S. aureus* isolates were eradicated, and the patients initially harboring these organisms were deemed clinical successes. Thus, the successful eradication rate is 8/10 (80%) for critical *S. aureus* isolates.

The 95% confidence interval around the difference in clinical and critical pathogen bacteriologic efficacy at the patient level follows:

CLINICAL SUCCESS AND CRITICAL PATHOGEN ERADICATION
MO Critical Pathogen Evaluable: [-0.22, 0.49]

Using the DAIDP "two-tailed 95% confidence interval approach", the critical pathogen evaluable population confidence interval should cross zero and remain within a lower bound delta of -0.10. Therefore, this analysis does not establish the regulatory definition of equivalence.

D. SAFETY ASSESSMENT: Skin and Skin Structure Infections in Pediatric Patients

Medical Officer's Comments: To assess the safety of Unasyn in pediatric patients, the medical officer reviewed and analyzed the safety database provided by the applicant for patients enrolled in the skin and skin structure infection protocol (89CE20-0449). The medical officer also reviewed and analyzed the safety database provided by the applicant for patients enrolled in the periorbital/preseptal and facial cellulitis protocol (90CE20-0493), which was designed as a prospective, non-comparative open-label study. Although this study was terminated because of low enrollment, the medical officer reviewed the safety profiles of patients treated under this protocol in order to obtain additional information which could be useful in evaluating the safety of administration of Unasyn as monotherapy in pediatric patients. The information regarding the safety of patients studied under the protocols 89CE20-0449 and 90CE20-0493 has been taken from the applicant's report, which has been reviewed by the statisticians at the Food and Drug Administration for appropriateness and accuracy. Tables used in the subsequent review of safety parameters which have been imported from the applicant's report/summary of this protocol will be identified as such throughout the discussion.

Criteria for Inclusion in Safety Analyses

The applicant included any patient who received at least one dose of study drug in the safety analyses (intent to treat population).

1. SKIN AND SKIN STRUCTURE INFECTIONS DATABASE (Protocol 89CE20-0449)

Safety Parameters

Adverse Events

All adverse events occurring during and up to 30 days post-treatment were reviewed by the Pfizer Project Physician to determine if any should be classified as "serious." All deaths reported to Pfizer are included in the applicant's report regardless of timing. Serious adverse events were defined as those which met one or more of the following criteria:

The adverse event:

- was fatal (any known death was reported as a severe adverse event, even if it occurred more than 30 days post-treatment).
- was life-threatening or potentially life-threatening
- resulted in permanent disability
- required hospitalization or prolongation of a hospital stay
- involved cancer, a congenital anomaly, or the result of a drug overdose
- suggested significant hazard to the patient

A summary of serious adverse events by treatment regimen is presented below:

SERIOUS ADVERSE EVENTS BY TREATMENT REGIMEN FOR INTENT TO TREAT PATIENTS

	Treatment Regimen	
	Unasyn (N=154)	Cefuroxime (N=80)
Serious Adverse Event	N (%)	N (%)
Death	2 (1.3%)[1]	0 (0%)
Rehospitalization	0 (0%)	3 (3.8%)
Upper Airway Obstruction	0 (0%)	1 (1.2%)

[1] In one patient (patient number 89N0088-14), death was due to asphyxia, which occurred 2 days after the patient had completed transitional oral therapy. In the other patient (patient number 90N0094-2), death was due to cardiac arrest 6 months after the patient completed the study. Neither death was attributed by the investigator to study drug.

Medical Officer's Comments: A review of the 2 deaths that occurred in patients treated with Unasyn revealed:

1. (Patient number : The final report of the autopsy performed by the coroner in one patient ascribed the death to "asphyxia due to or as a consequence of neck compression", and cannot be attributed to therapy related to the previously diagnosed skin and skin structure infection.

2. (Patient number : The 12 month old patient who died of cardiac arrest 6 months after completing the study protocol had a history of multiple congenital cardiac defects, including D-transposition of the great vessels, single cardiac ventricle, dextrocardia, pulmonary atresia, tricuspid atresia, and atrial septal defect, and had had multiple surgeries to correct cardiac and diagphragmatic defects, and to place a gastic tube. Information available pertaining to the death indicates the cardiac arrest resulted from progressive bradycardia, which was due to severe encephalopathy resulting from multiple cardiac arrests which occurred over a 5 day period approximately 6 weeks prior to death. It should also be noted that when this patient was enrolled in the study protocol with a diagnosis of impetigo of the perineum and buttocks, he suffered from congestive heart failure, and had a history of episodes of ventricular tachycardia. Except for a two month period, the patient had been intubated and on a ventilator since birth, and remained on the ventilator at the start of the study protocol. The patient developed severe ventricular tachycardia approximately 5 hours after receiving his first dose of Unasyn, which the investigator attributed to concurrent illness (congenital cardiac defects and congestive heart failure) and concurrent medication (aminophylline given for wheezing, with a subsequent documented aminophylline level of 38.3). Cardiopulmonary rescuscitation was initiated, the patient was appropriately medicated, an external pacemaker was placed, and the patient returned to normal sinus rhythm. Approximately 24 hours later, the patient developed severe tonic clonic seizures which the investigator attributed to the same causes as the tachycardia. Phenobarbital was administered and the seizures abated. Neither adverse event was attributed to the study drug, and the patient received an 11 day course of Unasyn with a successful outcome, and no additional adverse events. Review of the clinical data suggests that both the cardiac arrest and associated seizures were most likely caused by the patient's underlying cardiac disease and concurrent medication administration.

Three patients treated with cefuroxime required rehospitalization. Two of these patients were rehospitalized for infection, and were considered clinical failures by the medical officer (patient numbers . The

third patient (patient number was rehospitalized for surgery to remove a retained foreign body at the initial SSTI site. This patient was considered not evaluable by the medical officer secondary to failure to diagnose the foreign body at the initial clinical presentation. One patient (patient number treated with cefuroxime for cervical adenitis and cellulitis developed upper airway obstruction. This patient was provided emergent respiratory support, received additional antimicrobial therapy, and was considered a clinical failure.

All other adverse events reported were recorded and tabulated by body sytem and treatment regimen. Adverse events in all patients enrolled in the SSTI study that occurred in greater than one patient in either treatment group during the study period were included. Table 30 (prepared by the applicant) compares the number of patients experiencing adverse events, by treatment regimen:

PROTOCOL 89CE20-6449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 30: OVERALL TOLERATION (ALL CAUSALITIES)

	AMPICILLIN/SULBACTAM	CEFUROXIME
TOTAL NO. OF PATIENTS	154	80
MEAN DURATION OF THERAPY (DAYS)	4.5	4.4
MEAN NUMBER OF DOSES	13.7	10.6
TOTAL NO. OF PATIENTS WITH ADVERSE EXPERIENCES		
- DURING STUDY DRUG (PARENTERAL) THERAPY	17 (11.0%)	10 (12.5%)
- DURING ENTIRE STUDY	28 (18.2%)	16 (20.0%)
TOTAL NO. OF ADVERSE EXPERIENCES #		
- DURING STUDY DRUG (PARENTERAL) THERAPY	27	13
- DURING ENTIRE STUDY	45	22
TOTAL NO. OF PATIENTS WITH SERIOUS ADVERSE EXPERIENCES		
- DURING ENTIRE STUDY	2 (1.3%)	4 (5.0%)
TOTAL NO. OF PATIENTS WITH DOSE OF STUDY DRUG REDUCED DUE TO ADVERSE EXPERIENCES	6 (0.6%)	1 (1.3%)
TOTAL NO. OF PATIENTS DISCONTINUED FROM PROTOCOL DUE TO ADVERSE EXPERIENCES	2 (1.3%)	1 (1.3%)
TOTAL NO. OF PATIENTS DISCONTINUED FROM PROTOCOL DUE TO DEATH	1 (0.6%)	0 (0.0%)

#EACH ADVERSE EXPERIENCE WAS COUNTED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT.

Medical Officer's Comments: The mean duration of therapy for patients assigned to each of the two treatment regimens (ampicillin/sulbactam and cefuroxime) was similar. The incidence of adverse events during the study drug (parenteral) therapy period and the entire drug (parenteral plus oral) therapy period were similar for ampicillin/sulbactam-treated patients when compared to cefuroxime-treated patients (*study drug therapy*: 17/154 (11.0%) patients vs 10/80 (12.5%) patients, p=0.90; *entire drug therapy*: 28/154 (18.2%) patients vs 16/80 (20.0%) patients, p=0.87). The rate of serious adverse events, including deaths, was examined and discussed in the previous section. The rate of patients discontinued from protocol due to adverse events will be discussed in a subsequent section.

Table 31 (prepared by the applicant) compares the incidence and severity of adverse events in ampicillin/sulbactam-treated patients and cefuroxime-treated patients by body system during the study drug therapy period:

PROTOCOL 89CE20-8449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 31: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES (GROUPED BY BODY SYSTEM) OCCURRING DURING STUDY DRUG (PARENTERAL) THERAPY.

	AMPICILLIN/SULBACTAM				CEFUROXIME			
ADVERSE EXPERIENCE BY BODY SYSTEM	PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	SEVERITY MODERATE	SEVERITY SEVERE	PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	SEVERITY MODERATE	SEVERITY SEVERE
TOTAL NO. PATIENTS	154				80			
NO. OF PTS. WITH ADVERSE EXPERIENCE	17				10			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	2 (1.3%)				1 (1.3%)			
BODY AS A WHOLE	5 (3.2%)	5	0	0	1 (1.3%)	1	0	0
CARDIOVASCULAR SYSTEM	1 (0.6%)	0	0	1	0 (0.0%)	0	0	0
DIGESTIVE SYSTEM	7 (4.5%)	6	1	0	7 (8.8%)	5	2	0
NERVOUS SYSTEM	4 (2.6%)	2	1	1	1 (1.3%)	1	0	0
RESPIRATORY SYSTEM	1 (0.6%)	1	0	0	1 (1.3%)	0	0	1
SKIN AND APPENDAGES	7 (4.5%)	4	3	0	3 (3.8%)	3	0	0

---- (END) ----

EACH BODY SYSTEM WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES ONE OR MORE DIFFERENT TYPES OF ADVERSE EXPERIENCE CLASSIFIED IN THAT BODY SYSTEM WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

Medical Officer's Comments: The incidence of adverse events for the body as a whole, and by organ system (cardiovascular, digestive, nervous, respiratory, and skin) are not statistically different for patients assigned to the two treatment regimens. Although not statistically significant, there is a trend towards increased adverse events of the digestive system for cefuroxime-treated patients when compared to ampicillin/sulbactam-treated patients (7/80 patients vs 7/154 patients, p= 0.14).

Table 32 (prepared by the applicant) compares the incidence and severity of adverse events in ampicillin/sulbactam-treated patients and cefuroxime-treated patients by specific descriptions of adverse events, by body system, during the study drug therapy period:

PROTOCOL 89CE20-0449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 32: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES OCCURRING DURING STUDY DRUG (PARENTERAL) THERAPY.

ADVERSE EXPERIENCE	AMPICILLIN/SULBACTAM PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	CEFUROXIME PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE
TOTAL NO. PATIENTS	154				64			
NO. OF PTS. WITH ADVERSE EXPERIENCE	17				10			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	2 (1.3%)				1 (1.3%)			
BODY AS A WHOLE								
HEADACHE	3 (1.9%)	3	0	0	0 (0.0%)	0	0	0
INJECT SITE REACT	1 (0.6%)	1	0	0	1 (1.3%)	1	0	0
MONILIA	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
CARDIOVASCULAR SYSTEM								
TACHYCARDIA VENT	1 (0.6%)	0	0	1	0 (0.0%)	0	0	0
DIGESTIVE SYSTEM								
DIARRHEA	3 (1.9%)	3	0	0	3 (3.8%)	2	1	0
VOMIT	2 (1.3%)	2	0	0	2 (2.5%)	1	1	0
CONSTIP	1 (0.6%)	1	0	0	1 (1.3%)	1	0	0
ANOREXIA	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
MONILIA ORAL	1 (0.6%)	0	1	0	0 (0.0%)	0	0	0
MELENA	0 (0.0%)	0	0	0	1 (1.3%)	1	0	0
NERVOUS SYSTEM								
NERVOUSNESS	1 (0.6%)	1	0	0	1 (1.3%)	1	0	0
CONVULS	1 (0.6%)	0	0	1	0 (0.0%)	0	0	0
DIPLOPIA	1 (0.6%)	0	1	0	0 (0.0%)	0	0	0
DIZZINESS	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
RESPIRATORY SYSTEM								
EPISTAXIS	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
DYSPNEA	0 (0.0%)	0	0	0	1 (1.3%)	0	0	1
SKIN AND APPENDAGES								
PRURITUS	3 (1.9%)	2	1	0	1 (1.3%)	1	0	0
URTICARIA	2 (1.3%)	1	1	0	0 (0.0%)	0	0	0

TABLE 32: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES OCCURRING DURING STUDY DRUG (PARENTERAL) THERAPY. (CONTINUED)

ADVERSE EXPERIENCE	AMPICILLIN/SULBACTAM PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	CEFUROXIME PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE
RASH	1 (0.6%)	0	1	0	2 (2.5%)	2	0	0
DERM CONTACT	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
ULCER SKIN	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0

---- (END) ----

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

Medical Officer's Comments: The incidence of specific adverse events are not statistically different for patients assigned to the two treatment regimens, with the incidence of each specific adverse event being small. The most common adverse events were related to the digestive system (diarrhea/vomiting) and skin and appendages system (pruritus/urticaria/rash) for both antimicrobial treatment regimens. Two adverse events that deserve mention and discussion are ventricular tachycardia (1) (cardiovascular system) and convulsions (1) (nervous system). The two adverse events, which occurred in the same patient, were most likely caused by significant underlying illnesses including congenital heart disease and cardiac failure, and as discussed previously, there were numerous other factors present at the time of the administration of the parenteral antimicrobial which were identified as contributing to or causing these adverse events.

Table 33 (prepared by the applicant) compares the incidence and severity of adverse events in ampicillin/sulbactam-treated patients and cefuroxime-treated patients by body system during the entire drug therapy period:

PROTOCOL 89CE20-0449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 33: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES (GROUPED BY BODY SYSTEM) OCCURRING DURING ENTIRE STUDY.

	AMPICILLIN/SULBACTAM				CEFUROXIME			
	PATIENT INCIDENCE	SEVERITY			PATIENT INCIDENCE	SEVERITY		
ADVERSE EXPERIENCE BY BODY SYSTEM	NO. PTS. (%)	MILD	MODERATE	SEVERE	NO. PTS. (%)	MILD	MODERATE	SEVERE
TOTAL NO. PATIENTS	154				80			
NO. OF PTS. WITH ADVERSE EXPERIENCE	28 (18.2%)				16 (20.0%)			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	2 (1.3%)				1 (1.3%)			
BODY AS A WHOLE	6 (3.9%)	5	1	0	3 (3.8%)	3	0	0
CARDIOVASCULAR SYSTEM	2 (1.3%)	0	0	2	0 (0.0%)	0	0	0
DIGESTIVE SYSTEM	10 (6.5%)	6	2	0	8 (10.0%)	6	2	0
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
NERVOUS SYSTEM	4 (2.6%)	2	1	1	1 (1.3%)	1	0	0
RESPIRATORY SYSTEM	1 (0.6%)	1	0	0	1 (1.3%)	0	0	1
SKIN AND APPENDAGES	17 (11.0%)	13	4	0	7 (8.8%)	5	2	0

---- (END) ----

EACH BODY SYSTEM WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES ONE OR MORE DIFFERENT TYPES OF ADVERSE EXPERIENCE CLASSIFIED IN THAT BODY SYSTEM WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

Medical Officer's Comments: The incidence of adverse events for the body as a whole, and by organ system (cardiovascular, digestive, nervous, respiratory, and skin) are not statistically different for patients assigned to the two treatment regimens. A trend (not statistically significant) towards increased adverse events of the digestive system remained for cefuroxime-treated patients when compared to ampicillin/sulbactam-treated patients.

Table 34 (prepared by the applicant) compares the incidence and severity of adverse events in ampicillin/sulbactam-treated patients and cefuroxime-treated patients by specific description of adverse experience, by body system, during the entire drug therapy period:

PROTOCOL 89CE26-6449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS
CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE
INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 34: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES OCCURRING DURING ENTIRE STUDY.

ADVERSE EXPERIENCE	AMPICILLIN/SULBACTAM PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	CEFUROXIME PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE
TOTAL NO. PATIENTS	154				80			
NO. OF PTS. WITH ADVERSE EXPERIENCE	28 (18.2%)				16 (20.0%)			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	2 (1.3%)				1 (1.3%)			
BODY AS A WHOLE								
HEADACHE	3 (1.9%)	3	0	0	0 (0.0%)	0	0	0
FEVER	1 (0.6%)	0	1	0	1 (1.3%)	1	0	0
INJECT SITE REACT	1 (0.6%)	1	0	0	1 (1.3%)	1	0	0
MONILIA	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
CHILLS	0 (0.0%)	0	0	0	1 (1.3%)	1	0	0
INJURY ACCID	0 (0.0%)	0	0	0	1 (1.3%)	1	0	0
CARDIOVASCULAR SYSTEM								
HEART ARREST	1 (0.6%)	0	0	1	0 (0.0%)	0	0	0
TACHYCARDIA VENT	1 (0.6%)	0	0	1	0 (0.0%)	0	0	0
DIGESTIVE SYSTEM								
DIARRHEA	6 (3.9%)	5	1	0	4 (5.0%)	3	1	0
VOMIT	4 (2.6%)	3	1	0	3 (3.8%)	2	1	0
CONSTIP	1 (0.6%)	1	0	0	1 (1.3%)	1	0	0
ANOREXIA	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
MONILIA ORAL	1 (0.6%)	0	1	0	0 (0.0%)	0	0	0
MELENA	0 (0.0%)	0	0	0	1 (1.3%)	1	0	0
METABOLIC AND NUTRITIONAL DISORDERS								
SGOT INC	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
NERVOUS SYSTEM								
NERVOUSNESS	1 (0.6%)	1	0	0	1 (1.3%)	1	0	0
CONVULS	1 (0.6%)	0	0	1	0 (0.0%)	0	0	0
DIPLOPIA	1 (0.6%)	0	1	0	0 (0.0%)	0	0	0
DIZZINESS	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
RESPIRATORY SYSTEM								
EPISTAXIS	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0

TABLE 34: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES OCCURRING DURING ENTIRE STUDY. (CONTINUED)

ADVERSE EXPERIENCE	AMPICILLIN/SULBACTAM PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	CEFUROXIME PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE
DYSPNEA	0 (0.0%)	0	0	0	1 (1.3%)	0	0	1
SKIN AND APPENDAGES								
RASH	8 (5.2%)	6	2	0	3 (3.8%)	3	0	0
PRURITUS	4 (2.6%)	3	1	0	1 (1.3%)	1	0	0
SKIN DIS	2 (1.3%)	2	0	0	1 (1.3%)	1	0	0
URTICARIA	2 (1.3%)	1	1	0	0 (0.0%)	0	0	0
DERM CONTACT	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
ULCER SKIN	1 (0.6%)	1	0	0	0 (0.0%)	0	0	0
ECZEMA	0 (0.0%)	0	0	0	1 (1.3%)	0	1	0
RASH MAC PAP	0 (0.0%)	0	0	0	1 (1.3%)	0	1	0

---- (END) ----

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

Medical Officer's Comments: The incidence of specific adverse events are not statistically different for patients assigned to the two treatment regimens, and the incidence of each adverse event is small. The most common adverse events were related to the digestive system (diarrhea/vomiting) and skin and appendages system (pruritus/urticaria/rash) for both antimicrobial treatment regimens. It should be noted that during the protocol, 3/154 Unasyn-treated patients, and 2/80 cefuroxime-treated patients received one or more antimicrobial doses by the IM route.

Discontinuations from Protocol Due to Adverse Events

DISCONTINUATIONS DUE TO ADVERSE EVENTS DURING THE STUDY DRUG THERAPY PERIOD BY TREATMENT REGIMEN FOR INTENT TO TREAT PATIENTS

	Treatment Regimen	
	Unasyn (N=154)	Cefuroxime (N=80)
Reason for Discontinuation	**N (%)**	**N (%)**
Rash	2 (1.3%)	1 (1.3%)

Medical Officer's Comments: Two Unasyn-treated patients and one cefuroxime-treated patient were discontinued from the study protocol during parenteral therapy administration due to the development of rash.

DISCONTINUATIONS DUE TO ADVERSE EVENTS DURING THE TRANSITIONAL ORAL THERAPY PERIOD BY TREATMENT REGIMEN FOR INTENT TO TREAT PATIENTS

	Treatment Regimen	
	Unasyn (N=154)	Cefuroxime (N=80)
Reason for Discontinuation	**N (%)**	**N (%)**
Rash	0 (0%)	1 (1%)
SGOT increased	1 (<1%)	0 (0%)
Vomiting/Diarrhea	0 (0%)	1 (1%)

Medical Officer's comments: Three patients (one patient in the Unasyn protocol and two patients in the cefuroxime protocol) discontinued oral follow-up therapy due to adverse events. Although these 3 patients discontinued oral therapy, they returned for the required follow-up visits and were considered to have completed the study protocol.

Patients Administered Ampicillin/Sulbactam Dose Above Recommended Range or for Duration Exceeding 14 days

Six patients in the ampicillin/sulbactam group received total daily doses of ampicillin/sulbactam greater than an applicant-defined maximum, which was the upper limit of the dose range recommended in the protocol (recommended range: 150-300 mg/kg/day), extended by 10% (i.e., maximum dose=330 mg/kg/day). In these patients receiving greater than the defined maximum ampicillin/sulbactam dosage, the following adverse events were noted:

Pt No.	**Adverse Event**
	oral monilia
	mild peeling of hands and feet
	decrease neutrophils (11%)
	elevated lymphocytes (74%)
	increased eosinophils (16%)

Protocol Deviations

Patients whose participation in the study resulted in a deviation from the criteria or procedures described in the protocol were identified. Seventeen patients were discontinued from the study protocol by the applicant due to protocol deviation. Additionally, a small number of patients at some centers were not randomized in chronological order, or other randomization errors occurred. None of these inadvertent deviations were considered by the applicant to have introduced any bias into the assignment of patients into the treatment groups, or to have resulted in the incorrect identification of the drug administered in any patient. The deviations from the randomization code were not considered sufficient reason to exclude any of the patients from the analyses of safety or efficacy. The following patients had some degree of deviation from the randomization scheme:

(not randomized in chronological order)
(not randomized in chronological order)
(incorrectly assigned to cefuroxime)
(incorrectly assigned to ampicillin/sulbactam)
(incorrectly assigned to cefuroxime)
(not randomized in chronological order)
(not randomized in chronological order)
(randomized incorrectly)
(randomized incorrectly)
(randomized incorrectly)

Medical Officer's Comments: Of the 10 patients who were randomized incorrectly, 8/10 (80%) patients were excluded from the efficacy analysis by the medical officer for other reasons. The medical officer considered the remaining two patients (patient numbers) evaluable for efficacy. If these two patients were excluded from the efficacy analysis, the 95% confidence interval around the true difference in the overall clinical success rates does not change from the 95% confidence interval including these two patients: [-0.18, 0.15] vs [-0.18, 0.14].

Laboratory Test Abnormalities

The following tables present all reported laboratory test abnormalities. The abnormalities were further categorized by the applicant as follows:

1=insignificant deviation (abnormal baseline)
2=insignificant deviation (normal baseline)
3=single abnormal value
4=normal/near normal with continued therapy
9=did not meet criteria for Categories 1-4

The Pfizer Project Physician reviewed the test results in Category 9. Based on this review, abnormal values were left as Category 9 or recategorized to one of the following:

5=documented laboratory error
6=probably related to concurrent illness
7=probably related to concurrent drugs
8=insignificant or not due to study drug, by Pfizer physician

Tests which were not reassigned and remained in Category 9 at the conclusion of this process were considered to exhibit a pattern of abnormal results which were "clinically significant and possibly related to study drug."

Table 37 (prepared by the applicant) presents all laboratory test abnormalities by abnormal category for ampicillin/sulbactam-treated and cefuroxime-treated patients:

PROTOCOL 89CE29-0449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

BLE 37: SUMMARY OF LABORATORY TEST ABNORMALITIES

UDY MEDICATION - AMPICILLIN/SULBACTAM

A TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (Z=)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY 1	2	3	4	5	6	7	8	9(Z==)	TOTAL
MATOLOGY												
HCT(HEMATOCRIT)	130	80(62)	28	18	2			2		8		58
HGB(HEMOGLOBIN)	130	87(67)	24	12	1	2		2		2		43
WBC (WHITE BLOOD COUNT)	130	102(78)	12	3	1			1		4	1(1)	26
RBC (RED BLOOD CELLS)	130	87(67)	24	17						2		43
NEUTROPHILS	119	48(40)	27	14	1	1		5		24	7(6)	71
LYMPHOCYTES	119	54(47)	25	5	1			6		24	2(2)	63
EOSINOPHILS	119	89(75)	4	9	1			2		10	4(3)	30
MONOCYTES	119	81(68)	10	12	1			7		7	1(1)	38
BASOPHILS	118	107(91)		4						7		11
PLATELETS	129	84(65)	25	5	1			7		5	2(2)	45
BANDS	105	68(65)	15	11	1			1		9		37
ATYPICAL LYMPHS	14	6(43)	1							7		8
RUM CHEMISTRY												
SGOT UNITS	131	104(62)	12	4						5	4(3)	25
SGPT UNITS	133	114(86)	10	3	1			1		1	3(2)	19
BUN	130	103(79)	5	22								27
T/BILIRUBIN	123	100(81)	10	10						3		23
CREATININE	133	113(85)	16	4								20
NA (SODIUM)	129	117(91)	4	8								12
CL (CHLORIDE)	130	114(88)	3	11	1					1		16
K (POTASSIUM)	128	121(95)	2	3			1			1		7
TAL			257	163	12	3	1	34		118	24	614

PERCENTAGE OF TOTAL PATIENTS WITH NORMAL TEST RESULTS
PERCENTAGE OF TOTAL PATIENTS WITH CATEGORY 9 ABNORMALITY

RATORY TEST CATEGORIES ARE-
INSIG DEVIATION/ABNL BASELINE
INSIG DEVIATION/NL BASELINE
SINGLE ABNL VALUE
4:NL/NEAR NL WITH CONT THERAPY
5:DOCUMENTED LAB ERROR
6:PROB RELATED TO CONC ILL
7:PROB RELATED TO CONC DRUGS
8:INSIG, NOT DUE TO RX, BY PHYSICIAN
9:CLIN SIG/POSS RELATED TO RX

PROTOCOL 89CE29-0449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 37: SUMMARY OF LABORATORY TEST ABNORMALITIES (CONTINUED)

STUDY MEDICATION - CEFUROXIME

LAB TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (Z=)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY 1	2	3	4	5	6	7	8	9(Z==)	TOTAL
HEMATOLOGY												
HCT(HEMATOCRIT)	65	44(74)	11	5						1		17
HGB(HEMOGLOBIN)	65	50(77)	10	3						1	1(2)	15
WBC (WHITE BLOOD COUNT)	65	45(69)	8	4	1			1		2	2(3)	24
RBC (RED BLOOD CELLS)	65	50(77)	12	3								15
NEUTROPHILS	58	30(52)	14	5	2			2		5	2(3)	28
LYMPHOCYTES	58	24(41)	20	5				2		7		34
EOSINOPHILS	58	35(60)	7	1				1		5	9(16)	23
MONOCYTES	58	42(72)	10	3				1		2		16
BASOPHILS	58	52(90)	1	3	1					1		4
PLATELETS	64	41(64)	10	4				3		5	1(2)	23
BANDS	52	37(71)	10	3				1		1		15
ATYPICAL LYMPHS	11	7(64)			1					3		4
SERUM CHEMISTRY												
SGOT UNITS	62	49(79)	4	3	2					4		13
SGPT UNITS	62	54(87)	4	4						1	3(5)	12
BUN	61	49(80)	4	4						2		12
T/BILIRUBIN	58	50(86)	4	4								8
CREATININE	61	49(80)	4	7	1							12
NA (SODIUM)	61	53(87)	1	6						1		8
CL (CHLORIDE)	61	55(90)	1	5								6
K (POTASSIUM)	59	51(86)	2	1	1					4		8
IND/BILIRUBIN	1	0(0)		1								1
TOTAL			157	76	9			11		45	16	294

PERCENTAGE OF TOTAL PATIENTS WITH NORMAL TEST RESULTS
PERCENTAGE OF TOTAL PATIENTS WITH CATEGORY 9 ABNORMALITY

LABORATORY TEST CATEGORIES ARE-
1:INSIG DEVIATION/ABNL BASELINE
2:INSIG DEVIATION/NL BASELINE
3:SINGLE ABNL VALUE
4:NL/NEAR NL WITH CONT THERAPY
5:DOCUMENTED LAB ERROR
6:PROB RELATED TO CONC ILL
7:PROB RELATED TO CONC DRUGS
8:INSIG, NOT DUE TO RX, BY PHYSICIAN
9:CLIN SIG/POSS RELATED TO RX

Medical Officer's Comments: For both ampicillin/sulbactam- and cefuroxime-treated patients, the most common laboratory abnormalities noted (independent of attribution) included changes in hematologic indices, including hematocrit, white blood cells and platelets, and changes in serum chemistry values, including liver enzymes, BUN/CR (blood urea nitrogen/creatinine), and electrolyte values. For ampicillin/sulbactam-treated patients, abnormal laboratory tests included: hematocrit: 50/130 (38%), white blood cell count: 28/130 (22%), neutrophils: 71/119 (60%), lymphocytes: 63/119 (53%), eosinophils: 30/119 (25%), monocytes: 38/119 (32%), platelets: 45/129 (35%), band forms: 37/104 (35%), SGOT: 23/131 (18%), SGPT: 19/133 (14%), total bilirubin; 23/123 (19%), BUN: 27/130 (21%), CR: 20/133 (15%). For cefuroxime-treated patients, abnormal laboratory tests included: hematocrit: 17/65 (26%), white blood cell count: 20/65 (31%), neutrophils: 28/58 (48%), lymphocytes: 34/58 (59%), eosinophils: 23/58 (40%), monocytes: 16/58 (28%), platelets: 23/64 (36%), band forms: 15/52 (29%), SGOT: 13/62 (21%), SGPT: 12/62 (19%), total bilirubin: 8/58 (14%), BUN: 12/61 (20%), CR: 12/61 (20%). It should be noted that cefuroxime-treated patients were more likely to experience laboratory test abnormalities associated with eosinophils when compared to ampicillin/sulbactam-treated patients (23/58 (40%) tests vs 30/119 (25%) tests, p=0.07). For all other indices, the rates of laboratory test abnormalities were not statistically different between treatment regimens.

Table 38 presents all laboratory test abnormalities considered to be possibly related to study drug administration by treatment regimen:

PROTOCOL 89CE26-0449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS
CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE
INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 38: ABNORMAL LABORATORY VALUES POSSIBLY RELATED TO STUDY MEDICATION

STUDY MEDICATION: AMPICILLIN/SULBACTAM

LABORATORY TEST	GRANT NO.	PATIENT NO.	NORMAL RANGE	UNIT	BASELINE VALUES	MOST ABNORMAL VALUES	CATEGORY NUMBER
WBC (WHITE BLOOD COUNT)			5 - 13	TH/MM3	11	3.6	9
NEUTROPHILS			12 - 32	%	45	8	9
			13 - 33	%	22	5	9
			25 - 70	%	50	12	9
			- - -	%	44	-	9
			55 - 70	%	83	24	9
			55 - 70	%	66	24	9
			55 - 70	%	41	19	9
LYMPHOCYTES			- - -	%	21	-	9
			25 - 35	%	31	62	9
EOSINOPHILS			0 - 4	%	4	16	9
			0 - 4	%	5	10	9
			0 - 4	%	1	14	9
			0 - 4	%	3	17	9
MONOCYTES			5 - 10	%	13	24	9
PLATELETS			150 - 400	TH/MM3	496	825	9
			150 - 400	MM3	416	714	9
SGOT UNITS			5 - 35	U/L	42	120	9
			5 - 35	U/L	120	415	9
			5 - 35	U/L	57	128	9
			10 - 45	U/L	-	105	9
SGPT UNITS			0 - 50	IU/L	30	206	9
			7 - 56	U/L	97	515	9
			7 - 56	U/L	31	163	9

LABORATORY TEST CATEGORIES ARE -

1:INSIG DEVIATION/ABNL BASELINE
2:INSIG DEVIATION/NL BASELINE
3:SINGLE ABNL VALUE
4:NL/NEAR NL WITH CONT THERAPY
5:DOCUMENTED LAB ERROR
6:PROB RELATED TO CONC ILL
7:PROB RELATED TO CONC DRUGS
8:INSIG, NOT DUE TO RX, BY PHYSICIAN
9:CLIN SIG/POSS RELATED TO RX

PROTOCOL 89CE26-0449
A MULTICENTER STUDY OF 2:1 AMPICILLIN/SULBACTAM (UNASYN) VERSUS
CEFUROXIME IN THE TREATMENT OF SKIN AND/OR SKIN STRUCTURE
INFECTIONS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS

TABLE 38: ABNORMAL LABORATORY VALUES POSSIBLY RELATED TO STUDY MEDICATION (CONTINUED)

STUDY MEDICATION: CEFUROXIME

LABORATORY TEST	GRANT NO.	PATIENT NO.	NORMAL RANGE	UNIT	BASELINE VALUES	MOST ABNORMAL VALUES	CATEGORY NUMBER
HGB(HEMOGLOBIN)			10.7 - 15.8	GM/DL	10.9	6.9	9
WBC (WHITE BLOOD COUNT)			5 - 13	TH/MM3	10.9	3.8	9
			5 - 14	TH/MM3	10.5	3.3	9
NEUTROPHILS			23 - 45	%	54.6	21	9
			32 - 54	%	35	20	9
EOSINOPHILS			0 - 10	%	10	35	9
			0 - 10	%	4	15	9
			0 - 10	%	9.4	22	9
			0 - 8	%	9	15	9
			1 - 4	%	1	10	9
			0 - 4	%	0	11	9
			0 - 4	%	0	15	9
			0 - 6	%	0	17	9
			0 - 5	%	7	20	9
PLATELETS			140 - 450	/UL	297	805	9
SGPT UNITS			7 - 40	U/L	40	79	9
			7 - 40	U/L	18	176	9
			7 - 40	U/L	45	193	9

LABORATORY TEST CATEGORIES ARE -

1:INSIG DEVIATION/ABNL BASELINE
2:INSIG DEVIATION/NL BASELINE
3:SINGLE ABNL VALUE
4:NL/NEAR NL WITH CONT THERAPY
5:DOCUMENTED LAB ERROR
6:PROB RELATED TO CONC ILL
7:PROB RELATED TO CONC DRUGS
8:INSIG, NOT DUE TO RX, BY PHYSICIAN
9:CLIN SIG/POSS RELATED TO RX

A summary of the laboratory test abnormalities considered by the Pfizer Project Physician to be "clinically significant and possibly related to study drug" (Category 9) is presented below, for those tests with an incidence greater than 2% in either treatment group:

LABORATORY TEST ABNORMALITIES CONSIDERED CLINICALLY SIGNIFICANT AND POSSIBLY RELATED TO STUDY DRUG BY TREATMENT REGIMEN FOR INTENT TO TREAT PATIENTS

	Treatment Regimen		
	Unasyn	Cefuroxime	
	# with Abn Reslts\ # with Reslts[1] (%)	# with Abn Reslts\ # with Reslts[1] (%)	p-value
Laboratory Test			
White blood cell count	1/130 (1%)	2/65 (3%)	0.26
Neutrophils	7/119 (6%)	2/58 (3%)	0.72
Eosinophils	4/119 (3%)	9/58 (16%)	0.01
SGOT	4/131 (3%)	0/62 (0%)	0.30
SGPT	3/133 (2%)	3/62 (5%)	0.40

[1]# with Abn Reslts\# with Reslts (%) = Number of patients with abnormal laboratory test results/number of patients with laboratory test results

Medical Officer's Comments: When laboratory test abnormalities considered clinically significant and possibly related to study drug were examined, it was found that cefuroxime-treated patients were more likely to experience laboratory test abnormalities associated with eosinophils than ampicillin/sulbactam-treated patients (9/58 (16%) patients vs 4/119 (3%) patients, p=0.01). It should also be noted that there is no statistically significant difference in rate of laboratory test abnormalities for liver function tests (SGOT, SGPT) in ampicillin/sulbactam- vs cefuroxime-treated patients.

2. PERIORBITAL/PRESEPTAL AND FACIAL CELLULITIS (PPFC) DATABASE

Safety Parameters

Adverse Events

All adverse events occurring during and up to 30 days post-treatment were reviewed by the Pfizer Project Physician to determine if any should be classified as "serious." All deaths reported to Pfizer are included in the applicant's report regardless of timing. Serious adverse events were defined as those which met one or more of the following criteria:

The adverse event:

- was fatal (any known death was reported as a severe adverse event, even if it occurred more than 30 days post-treatment).
- was life-threatening or potentially life-threatening
- resulted in permanent disability
- required hospitalization or prolongation of a hospital stay
- involved cancer, a congenital anomaly, or the result of a drug overdose
- suggested significant hazard to the patient

A summary of serious adverse events by treatment regimen is presented below:

SERIOUS ADVERSE EVENTS FOR STUDY DRUG (UNASYN) FOR INTENT TO TREAT PATIENTS

	Treatment Regimen Unasyn (N=58)
Serious Adverse Event	N (%)
Bacteremia and Meningitis[1]	1 (1.7%)

[1] This patient (patient number 90N0082-1), treated with Unasyn for facial cellulitis, developed nausea, vomiting, irritability, repeat positive blood cultures for *Haemophilus influenzae*, and a repeat lumbar puncture with high white blood cell count, and elevated protein; patient was considered a clinical failure, and was removed from the protocol.

Medical Officer's Comments: The rate of serious adverse events in the PPFC protocol (1.7%) is similar to the rate reported for the SSTI protocol (1.3%).

All other adverse events reported were recorded and tabulated by body sytem and treatment regimen. Adverse events in all patients enrolled in the Periorbital/Preseptal and Facial Cellulitis study that occurred during the study period were included. Table 13 (prepared by the applicant) presents the number of patients experiencing adverse events:

STUDY : OPEN STUDY OF UNASYN IN THE TREATMENT OF PERIORBITAL/PRESEPTAL AND FACIAL CELLULITIS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS. - PROTOCOL 8493

TABLE 13: OVERALL TOLERATION (ALL CAUSALITIES)

	AMP/SUL
TOTAL NO. OF PATIENTS	58
MEAN DURATION OF THERAPY (DAYS)	4.4
MEAN NUMBER OF DOSES	14.0
TOTAL NO. OF PATIENTS WITH ADVERSE EXPERIENCES	
- DURING STUDY DRUG (PARENTERAL) THERAPY	10 (17.2%)
- DURING ENTIRE STUDY	11 (19.0%)
TOTAL NO. OF ADVERSE EXPERIENCES #	
- DURING STUDY DRUG (PARENTERAL) THERAPY	14
- DURING ENTIRE STUDY	15
TOTAL NO. OF PATIENTS WITH SERIOUS ADVERSE EXPERIENCES	
- DURING ENTIRE STUDY	1 (1.7%)
TOTAL NO. OF PATIENTS WITH DOSE OF STUDY DRUG REDUCED DUE TO ADVERSE EXPERIENCES	0 (0.0%)
TOTAL NO. OF PATIENTS DISCONTINUED FROM PROTOCOL DUE TO ADVERSE EXPERIENCES	1 (1.7%)
TOTAL NO. OF PATIENTS WHO DIED DUE TO AN ADVERSE EXPERIENCE	0 (0.0%)

#EACH ADVERSE EXPERIENCE WAS COUNTED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT.

Medical Officer's Comments: The mean duration of Unasyn therapy was 4.4 days, which is similar to the mean duration of Unasyn therapy for the SSTI protocol (4.5 days). The rate of patients experiencing adverse events during the study drug (parenteral Unasyn) therapy period and entire drug (parenteral plus oral therapy) therapy period were similar [10/58 (17.2%) and 11/58 (19.0%), respectively]. [These rates are not statistically different from the rates of patients experiencing adverse events during the study drug and entire drug therapy periods for the SSTI protocol (*study drug therapy period (Unasyn)*: 10/58 (17.2%) patients (PPFC) vs 17/154 (11.0%) patients (SSTI), p=0.33, *entire drug therapy period (Unasyn plus oral)*: 11/58 (19.0%) patients (PPFC) vs 28/154 (18.2%) patients (SSTI), p=0.95).] The rate of serious adverse events was examined and discussed in the previous section. The rate of patients discontinued from protocol due to adverse events will be discussed in a subsequent section.

Table 15 (prepared by the applicant) presents the incidence and severity of adverse events in ampicillin/sulbactam-treated patients during the study drug (parenteral) therapy period:

STUDY : OPEN STUDY OF UNASYN IN THE TREATMENT OF PERIORBITAL/PRESEPTAL AND FACIAL CELLULITIS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS. - PROTOCOL 6493

TABLE 15: INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES OCCURRING DURING STUDY DRUG (PARENTERAL) THERAPY.

	AMP/SUL			
	PATIENT INCIDENCE	SEVERITY		
ADVERSE EXPERIENCE	NO. PTS. (%)	MILD	MODERATE	SEVERE
TOTAL NO. PATIENTS	58			
NO. OF PTS. WITH ADVERSE EXPERIENCE	10			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	1 (1.7%)			
BODY AS A WHOLE				
FEVER	1 (1.7%)	0	1	0
DIGESTIVE SYSTEM				
VOMIT	6 (10.3%)	4	2	0
DIARRHEA	4 (6.9%)	2	2	0
NAUSEA	1 (1.7%)	0	1	0
SKIN AND APPENDAGES				
RASH	2 (3.4%)	2	0	0

---- (END) ----

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

Medical Officer's Comments: The most common adverse events associated with ampicillin/sulbactam administration in the PPFC protocol were related to the digestive system (vomiting/diarrhea) and skin and appendages system (rash). These were also the most common adverse events found to be associated with Unasyn administration in the SSTI protocol. The rate of adverse events of the digestive system (particularly vomiting) is statistically higher in Unasyn-treated patients in the PPFC protocol when compared to Unasyn-treated patients in the SSTI protocol (11/58 (19%) patients (PPFC) vs 7/154 (4.5%) patients (SSTI), p=0.002). The reason for this increased rate is unclear from the applicant's analyses and discussion. All doses of Unasyn were administered by the IV route to patients enrolled in this protocol.

Discontinuations from Protocol Due to Adverse Events

DISCONTINUATIONS DUE TO ADVERSE EVENTS DURING THE STUDY DRUG THERAPY PERIOD FOR INTENT TO TREAT PATIENTS

	Treatment Regimen Unasyn (N=58)
Reason for Discontinuation	**N (%)**
Diarrhea	1 (1.7%)

Medical Officer's Comments: One patient with lower left eyelid cellulitis (patient number 90N0083-93), who received Unasyn (maximum dose of 300 mg/kg/day) for 4 days, was discontinued from the protocol at the request of his mother, for diarrhea. The rate of Unasyn-treated patients discontinued due to adverse events during the PPFC protocol is similar to the rate in Unasyn-treated patients during the SSTI protocol (i.e, 1/58 patients (PPFC) vs 2/154 patients (SSTI).

Patients Administered Ampicillin/Sulbactam Dose Above Recommended Range or for Duration Exceeding 14 days

Two patients in the ampicillin/sulbactam group received total daily doses of ampicillin/sulbactam greater than an applicant-defined maximum, which was the upper limit of the dose range recommended in the protocol (recommended range: 150-300 mg/kg/day), extended by 10% (i.e., maximum dose=330 mg/kg/day). In these patients receiving greater than the defined maximum ampicillin/sulbactam dosage, the following adverse events were noted:

Pt No.	Adverse Event
	rash (mild)
	candidal diaper raah

Laboratory Test Abnormalities

The following tables present all reported laboratory test abnormalities. The abnormalities were further categorized by the applicant as follows:

1=insignificant deviation (abnormal baseline)
2=insignificant deviation (normal baseline)
3=single abnormal value
4=normal/near normal with continued therapy
9=did not meet criteria for Categories 1-4

The Pfizer Project Physician reviewed the test results in Category 9. Based on this review, abnormal values were left as Category 9 or recategorized to one of the following:

5=documented laboratory error
6=probably related to concurrent illness
7=probably related to concurrent drugs
8=insignificant or not due to study drug, by Pfizer physician

Tests which were not reassigned and remained in Category 9 at the conclusion of this process were considered to exhibit a pattern of abnormal results which was "clinically significant and possibly related to study drug."

Table 18 (prepared by the applicant) presents all laboratory test abnormalities by abnormal category for ampicillin/sulbactam-treated patients:

STUDY : OPEN STUDY OF UNASYN IN THE TREATMENT OF PERIORBITAL/PRESEPTAL AND FACIAL CELLULITIS OF BACTERIAL ETIOLOGY IN HOSPITALIZED PEDIATRIC PATIENTS. - PROTOCOL 0493

TABLE 18: SUMMARY OF LABORATORY TEST ABNORMALITIES

STUDY MEDICATION - AMP/SUL

LAB TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (%*)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY 1	2	3	4	5	6	7	8	9(%**)	TOTAL
HEMATOLOGY												
HCT(HEMATOCRIT)	48	35(73)	6	4						1	2(4)	13
HGB(HEMOGLOBIN)	48	38(79)	4	3	1						2(4)	10
WBC (WHITE BLOOD COUNT)	48	41(85)	5	1							1(2)	7
RBC (RED BLOOD CELLS)	48	33(69)	8	7								15
NEUTROPHILS	48	23(48)	7	1				5		7	5(10)	25
LYMPHOCYTES	48	25(52)	6	1	2			5		6	3(6)	23
EOSINOPHILS	48	28(58)	5	6	1					7	1(2)	20
MONOCYTES	48	25(52)	5	6				2		8	2(4)	23
BASOPHILS	48	38(79)	2	1						7		10
PLATELETS	48	21(44)	10	4				12		1		27
BANDS	47	27(57)	6	5						9		20
ATYPICAL LYMPHS	5	1(20)	1					1		2		4
SERUM CHEMISTRY												
SGOT UNITS	53	39(74)	7	4							3(6)	14
SGPT UNITS	53	34(64)	12	1							6(11)	19
BUN	51	30(59)	12	9								21
T/BILIRUBIN	49	41(84)	2	5						1		8
CREATININE	52	37(71)	11	4								15
NA (SODIUM)	52	48(92)	3	1								4
CL (CHLORIDE)	52	45(87)	1	6								7
K (POTASSIUM)	52	47(90)	1	1				3				5
DIR/BILIRUBIN	2	0(0)								2		2
TOTAL			114	70	4			28		51	25	292

* PERCENTAGE OF TOTAL PATIENTS WITH NORMAL TEST RESULTS
** PERCENTAGE OF TOTAL PATIENTS WITH CATEGORY 9 ABNORMALITY

LABORATORY TEST CATEGORIES ARE-
1:INSIG DEVIATION/ABNL BASELINE
2:INSIG DEVIATION/NL BASELINE
3:SINGLE ABNL VALUE
4:NL/NEAR NL WITH CONT THERAPY
5:DOCUMENTED LAB ERROR
6:PROB RELATED TO CONC ILL
7:PROB RELATED TO CONC DRUGS
8:INSIG, NOT DUE TO RX, BY PHYSICIAN
9:CLIN SIG/POSS RELATED TO RX

Medical Officer's Comments: For ampicillin/sulbactam-treated patients in the PPFC protocol, the most common laboratory abnormalities noted (independent of attribution) included changes in hematologic indices, including hematocrit, white blood cells and platelets, and changes in serum chemistry values, including liver enzymes, BUN/CR (blood urea nitrogen/creatinine), and electrolyte values. For ampicillin/sulbactam-treated patients in the PPFC protocol, abnormal laboratory tests included: hematocrit: 13/48 (27%), white blood cell count: 7/48 (15%), neutrophils: 25/48 (52%), lymphocytes: 23/48 (48%), eosinophils: 20/48 (42%), monocytes: 23/48 (48%), platelets: 27/48 (56%), band forms: 20/47 (43%), SGOT: 14/53 (26%), SGPT: 19/53 (36%), total bilirubin; 8/49 (16%), BUN: 21/51 (41%), CR: 15/52 (29%). It should be noted that Unasyn-treated patients in the PPFC protocol were more likely than Unasyn-treated patients in the SSTI protocol to experience laboratory test abnormalities associated with eosinophils, monocytes, platelets, SGPT, BUN and CR.

A summary of the laboratory test abnormalities considered by the Pfizer Project Physician to be "clinically significant and possibly related to study drug" (Category 9) is presented below, for those tests with an incidence greater than 2% among all patients:

LABORATORY TEST ABNORMALITIES CONSIDERED CLINICALLY SIGNIFICANT AND POSSIBLY RELATED TO STUDY DRUG (UNASYN) FOR INTENT TO TREAT PATIENTS

	Treatment Regimen Unasyn # with Abn Reslts\ # with Reslts[1] (%)
Laboratory Test	
Hematocrit	2/48 (4%)
Neutrophils	5/48 (10%)
Monocytes	2/48 (4%)
Lymphocytes	3/48 (6%)
SGOT	3/53 (6%)
SGPT	6/53 (11%)

[1]# with Abn Reslts\# with Reslts (%) = Number of patients with abnormal laboratory test results/number of patients with laboratory test results

Medical Officer's Comments: When laboratory test abnormalities considered clinically significant and possibly related to study drug were examined, it was found that Unasyn-treated patients experienced laboratory abnormalities associated with hematocrit, neutrophils, monocytes, lymphocytes, and liver function tests (SGOT, SGPT).

Medical Officer's Final Comments on Safety Analyses for SSTI:

The rate of serious adverse events and number of patients discontinued from the study protocol secondary to the development of an adverse event in the skin and skin structure infeciton safety database appear to be similar for both treatment regimens. Additionally, the incidence of adverse events by body system for both the study drug therapy and entire drug therapy period appear to be similar for patients in both treatment regimens, with the exception of an increased incidence of laboratory tests abnormalities associated with eosinophils in cefuroxime-treated vs ampicillin/sulbactam-treated patients. Laboratory abnormalities felt to be possibly related to Unasyn administration included abnormalities in white blood cell count, neutrophils, eosinophils, SGOT and SGPT--all adverse laboratory changes noted in adult patients and contained in the adverse reactions portion of the current Unasyn package insert.

The results of the analysis of the safety database for the PPFC protocol demonstrate similar rates of serious adverse events, rates of discontinuation from protocol due to adverse events, and incidence of adverse events for Unasyn-treated patients in the PPFC protocol compared to Unasyn-treated patients in the SSTI protocol, with one exception--Unasyn-treated patients in the PPFC protocol experienced an increased incidence of adverse events of the digestive system when compared to patients in the SSTI protocol. Laboratory abnormalities felt to be possibly related to Unasyn administration included abnormalities in hematocrit, neutrophils, monocytes, lymphocytes, SGOT and SGPT--all adverse laboratory changes noted in adult patients and contained in the adverse reactions portion of the current Unasyn package insert.

E. DISCUSSION/CONCLUSIONS

Using applicant-defined evaluability criteria and efficacy outcome definitions; the applicant reported 59/59 (100%) clinical improvements plus cures for Unasyn-treated evaluable patients, and 39/39 (100%) clinical improvements plus cures for cefuroxime-treated evaluable patients. The FDA statistician, Dr. Srinivasan, calculates that using the rates of clinical efficacy reported by the applicant, the clinical responses in the Unasyn and cefuroxime group are not significantly different, with a 95% confidence interval for the difference (Unasyn - Cefuroxime) of (-0.021,0.021). In terms of the applicant's reported bacteriologic efficacy, the two groups were also found not to be statistically different, with 84/89 (94.4%) of the pathogens isolated from the 59 evaluable Unasyn-treated patients and 54/55 (98%) of the pathogens isolated from the 39 evaluable cefuroxime-treated patients being eradicated, with the 95% confidence interval for the difference (Unasyn - Cefuroxime) of (-0.112,0.036). These confidence intervals do not satisfy the Guidelines of the Division of Anti-Infective Drug and Drug Products (DAIDP), which require the confidence intervals to cross zero and to remain within a lower bound delta of -0.10.

Using the medical officer-defined evaluability criteria and efficacy outcome definitions, there were 51/60 (85%) clinical successes in the clinically evaluable Unasyn-treated group, and 34/39 (87.2%) clinical successes in the clinically evaluable cefuroxime-treated group, with the 95% confidence interval for the difference between the clinical success rates for Unasyn and cefuroxime-treated patients being (-.18, 0.14). These results suggest that there is no significant difference in clinical outcome between the two treatment groups, but fail to satisfy the Guidelines of DAIDP; for clinical success rates from 80-90%, the division requires that the confidence interval cross zero and remain within a lower bound delta of -0.15. Similarly, analysis of the fully evaluable patient population demonstrated 26/28 (92.8%) successes in the Unasyn-treated group, and 22/24 (91.7%) successes in the cefuroxime-treated group, with the 95% confidence interval for the difference between success rates for Unasyn and cefuroxime-treated patients being (-0.17, 0.20), when the guidelines stipulate that in this instance the confidence interval should remain within a lower bound delta of -0.10. Analysis of the critical pathogen evaluable patient population demonstrated 15/16 (93.8%) successes in the Unasyn-treated group, and 8/10 (80%) successes in the cefuroxime-treated group, with the 95% confidence interval for the difference between success rates for Unasyn and cefuroxime-treated patients being (-0.22, 0.49), which also does not satisfy the DAIDP Guidelines for establishing therapeutic equivalence.

In the medical officer's evaluation of microbiologic efficacy, the 95% confidence interval around the difference in overall bacteriologic eradication rates for Unasyn- and cefuroxime-treated fully evaluable patients was (-0.12, 0.22), demonstrating a lower bound delta just slightly in excess of the required -0.10. In the critical pathogen evaluable patients, the 95% confidence intervals around the difference in overall bacteriologic eradication and critical pathogen eradication for Unasyn- and cefuroxime-treated patients were (-0.10, 0.55) and (-0.22, 0.49), respectively. Thus, the confidence interval around the difference in overall bacteriologic eradication for the critical pathogen evaluable patients fulfills the DAIDP requirements, and the confidence interval around the difference in critical pathogen bacteriologic eradication does not fulfill the DAIDP requirements for establishment of therapeutic equivalence.

Evaluation of the statistical significance of the results of this SSTI trial is difficult because of the small number of patients available for efficacy analysis, and overall the calculated 95% confidence intervals for the difference in clinical success and bacteriologic eradication rates between the

Unasyn- and cefuroxime-treated patients are too wide to establish therapeutic equivalence by present regulatory standards. However, this study is supportive of the comparative efficacy and safety of Unasyn when compared to cefuroxime in the treatment of SSTI in pediatric patients at the dosage regimen used. Since Unasyn has an FDA-approved indication for SSTI in adults--with substantial data available for safety and efficacy analysis in the adult population--, and the pathophysiology and microbiology of SSTI in adults and children is similar, it would seem advantageous to invoke the recently promulgated "Pediatric Rule" (21 CFR Part 201 "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule, December 13, 1994), in an effort to utilize these available data to promote safer and more effective use of prescription drugs in the pediatric population.

This final rule, which applies to prescription drug products (including biological prescription drug products), amends FDA regulations pertaining to the content and format of prescription drug labeling in §201.57 by revising the current "Pediatric use" subsection (§201.57(f)(9)) to allow a broader basis for the inclusion of information about the use of a drug in the pediatric population. The ruling recognizes several methods of establishing substantial evidence to support pediatric labeling claims, including relying, in certain cases, on studies carried out in adults. Sponsors are asked to reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and if appropriate, submit a supplemental application to comply with new §201.57(f)(9)(iv) by December 13, 1996. This action responded to concerns in FDA and elsewhere that current prescription drug labeling often does not contain adequate information about the use of drugs in the pediatric population.

The reasoning of the final rule was that the continuing absence of pediatric use information in prescription drug labeling may be due in part to the impression, perhaps conveyed by the existing regulation, that pediatric claims must always be based on adequate and well-controlled studies conducted in the pediatric population. Given the many problems associated with the testing of drugs in the pediatric population (e.g., obtaining informed consent for tests not directly of benefit to the child, use of placebo controls in a vulnerable population), studies meeting this standard are often difficult to obtain. Under the final rule, products may be labeled for pediatric use based on adequate and well-controlled studies in adults together with other information supporting pediatric use (e.g., pharmacokinetic data, safety data, pharmacodynamic data).

The major provisions of the final rule are summarized as follows:

" ...The final rule continues to permit a specific pediatric indication (i.e., an indication different from those approved in adults) supported by adequate and well-controlled studies in the appropriate pediatric population, to be described under the "Indications and Usage" section of the labeling, with the appropriate pediatric dosage given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling must include any limitations on the pediatric indication, need for specific monitoring, specific hazards of the drug, differences between pediatric and adult responses to the drug, and other information related to the safe and effective use of the drug in pediatric patients.

If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and

Administration" section of the labeling.....
.....A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted."

In summary, although the SSTI study does not establish therapeutic equivalence as defined by the DAIDP, the study is supportive of the efficacy and safety of Unasyn in the treatment of SSTI in pediatric patients at the dosage regimen used, and approval of the skin and skin structure infection indication in pediatric patients under the Final Rule is strongly supported by the results submitted for this study protocol.

F. RECOMMENDATIONS: Skin and Skin Structure Infections Indication in Pediatric Patients

The medical officer recommends that the treatment indication for skin and skin structure infections in pediatric patients should be granted under the recently promulgated "Pediatric Rule" (21 CFR Part 201 "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule", December 13, 1994).

Pages 58-107
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Indication

III. COMPREHENSIVE SAFETY REVIEW

A. CUMULATIVE SAFETY ANALYSIS

In addition to the individual analyses of individual protocol databases, the applicant also submitted a cumulative safety analysis database (from the three U.S. pediatric studies, 89CE20-0449, 89CE20-0450, and 90CE20-0493). This database includes U.S. safety data on the cumulative pediatric supplemental database of 541 patients, 487 patients originally presented in the NDA (filed 11/30/93) plus an additional 54 patients (from patients who completed or prematurely discontinued from the study between May 19, 1992 and May 1, 1993) whose data have since been entered into the database after the data cut-off for the original submission (post-cut-off patients). Of the additional 54 patients, 33 received ampicillin/sulbactam and 21 received comparative agents. Thus, a total of 376 patients received ampicillin/sulbactam and 165 received comparative agents.

Medical Officer's Comments: The information regarding the safety of patients studied under the three treatment protocols initially enrolling patients, (SSTI), with additional information gathered from patients enrolled subsequent to the NDA efficacy supplement submission has been taken from the applicant's report, which has been reviewed by the statisticians at the Food and Drug Administration for appropriateness and accuracy. Tables used in the subsequent cumulative review of safety parameters which have been imported from the applicant's report/summary of these protocols will be identified as such throughout the discussion. Below is a listing of the cumulative number of patients enrolled in the U.S. studies, by protocol number, and including the number of patients analysed during the NDA and post-NDA periods.

LISTING OF U.S. STUDIES*

Protocol Number	sNDA Number of Patients	Post-sNDA Number of Patients	Cumulative Number of Patients
89CE20-0449			
Amp/Sul	154	29	183
Cefuroxime	80	17	97
89CE20-0450			
Amp/Sul	131	4	135
Amp/Clind/Amino	64	4	68
90CE20-0493			
Amp/Sul	58	0	58

* Studies included in this safety update are as follows: Protocol 89CE20-0449, Protocol 90CE20-0493, and Protocol 89CE20-0450; however, no additional patients were entered from Protocol 90CE20-0493 during the post-sNDA time period.

Adverse Events

SERIOUS ADVERSE EVENTS

The rate of serious adverse events in all Unasyn-treated patients was 16/376 (4%) patients (one post-cut-off patient had a serious adverse event: cellulitis secondary to herpes simplex infection [patient number protocol 89CE20-0450]). Additionally, two patients receiving comparative agents experienced serious adverse events (rehospitalization [patient number protocol 89CE20-0450] and febrile seizures [patient number protocol 89CE20-0449]). Thus, the cumulative rate of serious adverse events for comparative agent-treaed patients was 10/165 (6%) patients.

Medical Officer's Comments: No significant increased rate of serious events associated with Unasyn administration was demonstrated in the cumulative safety analysis. No deaths were reported among the 54 post-cut-off patients.

Table 4A (prepared by the applicant) presents the incidence and severity of adverse events experienced by all Unasyn-treated patients:

TABLE 4A: CUMULATIVE INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES (GROUPED BY BODY SYSTEM): ALL U.S. STUDIES[1]
ALL AMP/SUL PATIENTS

ADVERSE EXPERIENCE BY BODY SYSTEM	AMPICILLIN/SULBACTAM — PATIENT INCIDENCE NO. PTS. (%)	SEVERITY — MILD	MODERATE	SEVERE
TOTAL NO. PATIENTS	376			
NO. OF PTS. WITH ADVERSE EXPERIENCE	70			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	7 (1.9%)			
BODY AS A WHOLE	16 (4.3%)	11	5	0
CARDIOVASCULAR SYSTEM	3 (0.8%)	0	0	3
DIGESTIVE SYSTEM	42 (11.2%)	30	12	0
HEMIC AND LYMPHATIC SYSTEM	0 (0.0%)	0	0	0
NERVOUS SYSTEM	4 (1.1%)	2	1	1
RESPIRATORY SYSTEM	2 (0.5%)	2	0	0
SKIN AND APPENDAGES	22 (5.9%)	17	5	0
SPECIAL SENSES	1 (0.3%)	0	0	1
UROGENITAL SYSTEM	10 (2.7%)	9	1	0

---- (END) ----

EACH BODY SYSTEM WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES ONE OR MORE DIFFERENT TYPES OF ADVERSE EXPERIENCE CLASSIFIED IN THAT BODY SYSTEM WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.
[1]INCLUDES PROTOCOLS 89CE20-0449, 89CE20-0450 AND 90CE20-0493. HOWEVER, NO ADDITIONAL PATIENTS WERE ENTERED FROM PROTOCOL 90CE20-0493 DURING THE POST-NDA TIME PERIOD.

Medical Officer's Comments: The overall incidence of adverse events among Unasyn-treated patients was 70/376 (19%). The most common adverse events included those involving the digestive system, the skin and skin appendages system, and the urogenital system. The overall incidence of adverse events, as well as the distribution of events by system, is also similar to the safety profiles for Unasyn-treated patients found during previous individual protocol analysis. The increased incidence of adverse events of the urogenital system can be attributed to patients in the IA protocol.

Table 5A (prepared by the applicant) compares the incidence and severity of adverse events in Unasyn-treated patients and comparative agent-treated patients by body system:

TABLE 5A: CUMULATIVE INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES (GROUPED BY BODY SYSTEM): U.S. STUDIES[1]
AMP/SUL AND COMPARATIVE AGENTS IN CONTROLLED STUDIES[2]

ADVERSE EXPERIENCE BY BODY SYSTEM	AMPICILLIN/SULBACTAM PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	COMPARATIVE AGENT PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE
TOTAL NO. PATIENTS	318				165			
NO. OF PTS. WITH ADVERSE EXPERIENCE	60				36			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	6 (1.9%)				4 (2.4%)			
BODY AS A WHOLE	15 (4.7%)	11	4	0	8 (4.8%)	5	3	0
CARDIOVASCULAR SYSTEM	1 (0.3%)	0	0	1	1 (0.6%)	1	0	0
DIGESTIVE SYSTEM	34 (10.7%)	26	8	0	22 (13.3%)	16	6	0
HEMIC AND LYMPHATIC SYSTEM	0 (0.0%)	0	0	0	1 (0.6%)	1	0	0
NERVOUS SYSTEM	4 (1.3%)	2	1	1	2 (1.2%)	2	0	0
RESPIRATORY SYSTEM	2 (0.6%)	2	0	0	1 (0.6%)	0	0	1
SKIN AND APPENDAGES	20 (6.3%)	15	5	0	11 (6.7%)	9	2	0
SPECIAL SENSES	1 (0.3%)	0	0	1	0 (0.0%)	0	0	0
UROGENITAL SYSTEM	10 (3.1%)	9	1	0	1 (0.6%)	1	0	0

---- (END) ----

EACH BODY SYSTEM WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES ONE OR MORE DIFFERENT TYPES OF ADVERSE EXPERIENCE CLASSIFIED IN THAT BODY SYSTEM WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.
[1]INCLUDES PROTOCOLS 89CE20-0449 AND 89CE20-0450.
[2]COMPARATIVE AGENTS INCLUDE CEFUROXIME AND AMPICILLIN/CLINDAMYCIN/AMINOGLYCOSIDE.

Medical Officer's Comments: The incidence of adverse events for the body as a whole, and by organ system (cardiovascular, digestive, hemic and lymphatic, nervous, respiratory, skin, special senses) are not statistically different for patients assigned to Unasyn vs comparative agent treatment regimens. There is a trend towards increased adverse events of the urogenital system for Unasyn-treated patients when compared to comparative agent-treated patients (10/318 patients vs 1/165 patients, p=0.11). Note that this table includes 318 Unasyn-treated patients (total Unasyn-treated patients=376), only those enrolled in controlled clinical trials.

Discontinuations from Protocol Due to Adverse Events

A total of 6/376 (1.6%) Unasyn-treated patients were discontinued from protocol due to adverse events. All patients have been discussed in previous individual protocol safety reviews.

Patients Administered Ampicillin/Sulbactam Dose Above Recommended Range or for Duration Exceeding 14 days

Ten Unasyn-treated patients received total daily doses of ampicillin/sulbactam greater than an applicant-defined maximum, which was the upper limit of the dose range recommended in the protocol (recommended range: mg/kg/day), extended by 10% (i.e., maximum dose=330 mg/kg/day). All patients have been discussed in previous individual protocol safety reviews.

Laboratory Test Abnormalities

Table 10A (prepared by the applicant) presents all laboratory test abnormalities by abnormal category for all Unasyn-treated patients:

TABLE 10A: CUMULATIVE SUMMARY OF LABORATORY TEST ABNORMALITIES: ALL U.S. STUDIES[1]
ALL AMP/SUL PATIENTS

STUDY MEDICATION - AMP/SUL

LAB TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (%)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY									
			1	2	3	4	5	6	7	8	9(%)	TOTAL
HEMATOLOGY												
HCT(HEMATOCRIT)	320	189(59)	45	41	5	7		21		10	2(1)	131
HGB(HEMOGLOBIN)	320	217(68)	34	32	6	5		22		2	2(1)	103
WBC (WHITE BLOOD COUNT)	321	236(74)	47	8	5	1		12		10	2(1)	85
RBC (RED BLOOD CELLS)	320	202(63)	44	40	2	2		6		2		116
NEUTROPHILS	307	107(35)	99	16	9	4		30		28	14(5)	200
LYMPHOCYTES	307	118(38)	115	12	5			20		31	8(3)	189
EOSINOPHILS	305	217(71)	35	21	2			2		20	8(3)	88
MONOCYTES	307	197(64)	31	31	6			21		18	3(1)	110
BASOPHILS	300	252(84)	21	13						14		48
PLATELETS	310	176(57)	43	25	1			51		8	6(2)	134
BANDS	281	177(63)	41	27	3			5		27	1(0)	104
ATYPICAL LYMPHS	25	10(40)	3					1		10	1(4)	15
SERUM CHEMISTRY												
SGOT UNITS	304	231(76)	27	18	8	1				9	10(3)	73
SGPT UNITS	307	243(79)	27	12	3	1		1		10	10(3)	64
BUN	313	203(65)	33	75	1					1		110
T/BILIRUBIN	290	241(83)	16	26	1					5	1(0)	49
CREATININE	314	253(81)	36	25								61
NA (SODIUM)	317	266(84)	22	29								51
CL (CHLORIDE)	317	272(86)	9	31	2					3		45
K (POTASSIUM)	314	287(91)	5	8	5		2	3		4		27
DIR/BILIRUBIN	6	3(50)								3		3

TABLE 10A: CUMULATIVE SUMMARY OF LABORATORY TEST ABNORMALITIES: ALL U.S. STUDIES[1]
ALL AMP/SUL PATIENTS (CONTINUED)

STUDY MEDICATION - AMP/SUL

LAB TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (%*)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY									
			1	2	3	4	5	6	7	8	9(%**)	TOTAL
URINALYSIS												
PH:URINE	86	77(90)			2					7		9
SPECIFIC GRAVITY:URINE	83	74(89)	1		2					6		9
RED BLOOD CELL HPF URINE	59	57(97)			2							2
WHITE BLOOD CELL HPF URIN	64	60(94)			1			1		2		4
MISCELLANEOUS												
UROBILINOGEN	15	9(60)								6		6
TOTAL			736	518	69	21	2	196		236	68	1836

* PERCENTAGE OF TOTAL PATIENTS WITH NORMAL TEST RESULTS
** PERCENTAGE OF TOTAL PATIENTS WITH CATEGORY 9 ABNORMALITY

LABORATORY TEST CATEGORIES ARE-
1:INSIG DEVIATION/ABNL BASELINE
2:INSIG DEVIATION/NL BASELINE
3:SINGLE ABNL VALUE
4:NL/NEAR NL WITH CONT THERAPY
5:DOCUMENTED LAB ERROR
6:PROB RELATED TO CONC ILL
7:PROB RELATED TO CONC DRUGS
8:INSIG, NOT DUE TO RX, BY PHYSICIAN
9:CLIN SIG/POSS RELATED TO RX

[1]INCLUDES PROTOCOLS 89CE20-0449, 89CE20-0450 AND 90CE20-0493. HOWEVER, NO ADDITIONAL PATIENTS WERE ENTERED FROM PROTOCOL 90CE20-0493 DURING THE POST-NDA TIME PERIOD.

Medical Officer's Comments: For all Unasyn-treated patients, the most common laboratory abnormalities noted (independent of attribution) included changes in hematologic indices, including hematocrit, white blood cells and platelets, and changes in serum chemistry values, including liver enzymes, BUN/CR (blood urea nitrogen/creatinine), and electrolyte values. Abnormal tests included: hematocrit: 131/320 (41%), white blood cell count: 85/321 (26%), neutrophils: 200/307 (65%), lymphocytes: 189/307 (62%), atypical lymphocytes: 15/25 (60%), eosinophils: 88/305 (29%), monocytes: 110/307 (36%), platelets: 134/310 (43%), band forms: 104/281 (37%), SGOT: 73/304 (24%), SGPT: 64/307 (21%), total bilirubin: 49/290 (17%), BUN: 110/313 (35%), CR: 61/314 (19%). No novel or unexpected laboratory test abnormalities were revealed in the cumulative safety analysis. All test abnormalities, except atypical lymphocytes, are described in the current Unasyn package insert.

Table 10C presents all laboratory test abnormalities considered to be possibly related to Unasyn administration:

TABLE 10C: CUMULATIVE INCIDENCE OF CLINICALLY SIGNIFICANT RELATED LABORATORY ABNORMALITIES: ALL U.S. STUDIES[3] ALL AMP/SUL[1]

	AMPICILLIN/SULBACTAM	
LAB TEST	TOTAL NUMBER PATIENTS	NUMBERS (%) ABNORMAL
HEMATOLOGY		
HCT(HEMATOCRIT)	320	2 (1)
HGB(HEMOGLOBIN)	320	2 (1)
WBC (WHITE BLOOD COUNT)	321	2 (1)
NEUTROPHILS	307	14 (5)
LYMPHOCYTES	307	8 (3)
EOSINOPHILS	305	8 (3)
MONOCYTES	307	3 (1)
PLATELETS	310	6 (2)
BANDS	281	1 (0)
ATYPICAL LYMPHS	25	1 (4)
SERUM CHEMISTRY		
SGOT UNITS	304	10 (3)
SGPT UNITS	307	10 (3)
T/BILIRUBIN	290	1 (0)
TOTAL		66

[1]INCLUDES PROTOCOLS 89CE20-0449, 89CE20-0450 AND 90CE20-0493. HOWEVER, NO ADDITIONAL PATIENTS WERE ENTERED FROM PROTOCOL 90CE20-0493 DURING THE POST-NDA TIME PERIOD.
[3]THIS INCIDENCE OCCURRED IN 45 PATIENTS.

A summary of the laboratory test abnormalities considered by the Pfizer Project Physician to be "clinically significant and possibly related to study drug" (Category 9) is presented below, for those tests with an incidence greater than 2% in either treatment group:

LABORATORY TEST ABNORMALITIES CONSIDERED CLINICALLY SIGNIFICANT AND POSSIBLY RELATED TO STUDY DRUG

	Treatment Regimen Unasyn # with Abn Reslts\ # with Reslts[1] (%)
Laboratory Test	
Neutrophils	14/307 (5%)
Lymphocytes	8/307 (3%)
Eosinophils	8/307 (3%)
Platelets	6/310 (2%)
Atypical Lymphocytes	1/25 (4%)
SGOT	10/304 (3%)
SGPT	10/307 (3%)

[1]# with Abn Reslts\# with Reslts (%) = Number of patients with abnormal laboratory test results/number of patients with laboratory test results

Medical Officer's Comments: When laboratory test abnormalities considered clinically significant and possibly related to Unasyn administration were examined, it was found that Unasyn-treated patients experienced abnormal laboratory tests related to neutrophils, lymphocytes, eosinophils, platelets atypical lymphocytes, and liver function tests (SGOT, SGPT). All test abnormalities, except atypical lymphocytes, are described in the current Unasyn package insert.

B. POST-MARKETING SURVEILLANCE

The applicant has also submitted a review of their post-marketing adverse events surveillance system. The applicant states that four pediatric patients had adverse events reported to Pfizer as of May 1, 1993. These events occurred during off-label use of ampicillin/sulbactam in pediatric patients in the United States, and none of the patients had a documented history of hypersensitivity or allergy to penicillin. The events occurring in these 4 patients are summarized in the following table (prepared by the applicant):

U.S. POST-MARKETING SPONTANEOUSLY REPORTED ADVERSE EXPERIENCES

Sex	Age (yrs)	Date of Onset	Event	Investigator's Causality	Action Taken	Outcome
Female[a]	6	June 6, 1991	Erythema (Rash erythematous) Facial edema	Not Available	Dose temporarily stopped	Resolved
Male[a]	4	Dec. 10, 1990	Urticaria	Not Available	Unknown	Resolved
Unknown[a]	10	Unknown	Anaphylaxis (Anaphylactoid reaction)	Not Available	Unknown	No data available
Female[b]	11	1989	Shock	Sepsis	Dose stopped	Resolved

a: Designated as a non-serious adverse experience by the sponsor.
b: Designated as a serious adverse experience by the sponsor.

Medical Officer's Comments: These spontaneously reported adverse events (facial edema/erythema, urticaria, anaphylaxis, and shock) are serious events which should be contained in product labeling. Facial swelling and erythema are contained in the current Unasyn package insert under *Systemic Adverse Reactions*. Urticaria is discussed in the current Unasyn package insert under *Hypersensitivity Reactions*. The risk of anaphylactic reactions in patients on penicillin therapy, and appropriate emergent management of such reactions, is discussed separately under the *Warnings* section of the current Unasyn package insert. Without data on the incidence/prevalence of off-label Unasyn use in pediatric patients in the United States, it is not possible to estimate the rate of such serious adverse events in pediatric patients receiving Unasyn therapy.

Medical Officer's Final Comments on Cumulative Safety Analysis:

The review of the cumulative safety database revealed no unexpected increases in serious adverse events for Unasyn-treated patients. Further, the incidence and distribution of adverse events were similar to those reported for Unasyn-treated patients in the individual protocols, and similar to the rates of adverse events in comparative agent-treated patients. Laboratory test abnormalities noted in Unasyn-treated patients, except for atypical lymphocytes, had been previously observed in adult patients, and are contained in the current Unasyn package insert. Post-marketing adverse events surveillance will allow the FDA to monitor the risk of systemic and hypersensitivity reactions in pediatric patients.

C. SAFETY REVIEW OF NON-U.S. STUDIES

The applicant also collected and analyzed safety data on pediatric studies conducted outside the United States. Although these diverse studies were not conducted as part of a centralized world-wide pediatric program, they were analyzed and submitted to provide supportive safety information on children exposed to parenterally administered ampicillin/sulbactam. Due to the manner in which these study data were collected (e.g., review of clinical reports and publications), individual data were not always available in some non-U.S. studies.

Four categories were established by the applicant to summarize the safety data from the non-U.S. reports and publications. The first category, Non-U.S. Studies with >50% Pediatric Patients, is the primary category of analysis of non-U.S. pediatric safety data. An additional three categories (Non-U.S. Studies with <50% Pediatric Patients, Non-U.S. Ongoing Studies, and Non-U.S. Discontinued Studies) were included to provide completeness in reporting of non-U.S. safety data in patients exposed to Unasyn. For the purposes of these non-U.S. analyses, the cut-off date for inclusion as completed studies was patients reported in clinical reports or publications issued as of March 25, 1992.

Medical Officer's Comments: The medical officer has reviewed the applicant's analyses on non-U.S. safety data. The medical officer finds that the first category, Non-U.S. Studies with >50% Pediatric Patients, is the most enlightening and important contribution to safety data in pediatric patients, and will discuss and summarize data from this category below:

Non-U.S. Studies with >50% Pediatric Patients

The first and primary category of non-U.S. safety data in pediatric patients included a summary of 49 completed non-U.S. studies in which more than 50% of the treated patients were under the age of 12 years (For a full listing of these clinical reports and publications, please see Appendix C, TABLE 1: LISTING OF STUDIES (NON-U.S.) [prepared by the applicant]. The studies

included in this category were primarily pediatric trials in which most, if not all, patients in each trial were less than 12 years old. In these 49 studies, children with skin and skin structure, intra-abdominal, respiratory tract, urinary tract, and other site infections were treated with Unasyn or a comparative agent. Seventeen studies were conducted in Japan, seven studies were conducted in Italy, five in France, three in Chile, and two each in the United Kingdom and Taiwan. One study was conducted in each of the following countries: Argentina, Belgium, Czechoslovakia, Germany, Greece, Korea, Mexico, Pakistan, Phillipines, Poland, Sweden, and Turkey.

Table 2g (prepared by the applicant) presents the demographic characteristics and extent of exposure to ampicillin/sulbactam in all non-U.S. studies with >50% pediatric patients:

TABLE 2g
DEMOGRAPHICS/EXTENT OF EXPOSURE TO AMP/SUL
ALL NON-US STUDIES WITH >50% PEDIATRIC PATIENTS

	All Amp/Sul*		Amp/Sul 2:1 Only (44 Studies)	
	(N)	(%)	(N)	(%)
Total No. of Patients	1649	100	1356	100
Sex				
Male	853	52	687	51
Female	711	43	584	43
Missing	85	5	85	6
Age Range**				
neonate - >60 yrs.	1630	99	1337	99
Unknown	19	1	19	1
Duration of Therapy				
1 dose - 44 days	1649	100	1356	100
Daily Dose:				
Range				
22.5 to 600 mg/kg	1559	95	1266	93
.75 to 12 g***	90	5	90	7
Unknown	0	-	0	-
Route:+#				
IV	1113	67	982	72
IM	152	9	152	11
IV/IM++	386	23	224	17

* Includes amp/sul in 1:1, 2:1, 3:1, 4:1, and 8:1 combinations and pen/sul in 3:1 and 4:1 combinations (six patients in Study 72-1 treated with pen/sul).

** In 47 studies, 122 amp/sul patients were between 0 and <3 months of age (in four studies all 93 amp/sul patients were under 3 months of age) and 1174 patients were between 3 months and <12 years of age. In seven studies, 242 patients were between 1 month and 18 years of age. In 13 studies, 39 patients were ≥12 years and ≤18 years of age. In two studies, 53 patients ranged in age from >6 years to >60 years. No age data were available for 19 patients (enrolled in four studies).

*** Only data available for Study SBT/AMP-PAK-87-001 PAKISTAN and adult patients in SBT/AMP-EED-87-001 CIS and *Jap. J. Antib.*, XLII (3): p. 579-593, March 1989.

\+ In Study SBT/AMP-NY-83-001 FRANCE, three patients received both IM and IV amp/sul and are counted in each category. In Study SBT/AMP-NY-83-005 Astruc, the route of administration was unknown for one patient.

\# 85 patients also received oral sultamicillin (tosylate salt of ampicillin and sulbactam, 1.5:1 combination) after receiving parenteral amp/sul for <1 to 11 days.

++ The exact route of administration, IV or IM, was not specified.

Medical Officer's Comments: A total of 1649 patients were treated in the 49 non-U.S. studies (clinical reports and publications). Of these patients, 1296 (79%) were reported as under 12 years of age, 281 (17%) were reported as less than or equal to 18 years of age, and age was either unknown or greater than 60 years in 72 patients (4%). The duration of Unasyn therapy in these patients ranged from 1 dose to 44 days, and the daily Unasyn dose for the majority of patients ranged from 22.5 to 600 mg/kg. Approximately 67 percent of patients (1113/1649) were treated with Unasyn by IV administration alone; approximately 33% of patients were treated with Unasyn by IM or combination IV/IM administration.

It should also be noted that a small number of studies in this group did not solely utilize the Unasyn 2:1 combination. Of the 49 studies, 44 studies (including 1356 patients) used only 2:1 Unasyn and 5 studies used other Unasyn formulations either alone or in addition to the 2:1 formulation.

Tables 13d and 13c (prepared by the applicant) present serious adverse events occurring in patients in the non-U.S. studies by treatment regimen:

TABLE 13d
DEATHS
ALL AMP/SUL AND ALL COMPARATIVE AGENTS
NON-U.S. STUDIES WITH >50% PEDIATRIC PATIENTS

Deaths	All Amp/Sul		Comparative Agents	
Total Number of Patients Treated with Amp/Sul# (All Combinations)	N	(%)	N	(%)
	1649	100	175	100
Total Number of Patients Who Died During Treatment	1	<1	0	-
Study: SBT/AMP-TR-86-002 (Amp/Sul 4:1 combination) Cause of death: Disseminated intravascular coagulation	1	<1	0	-

Includes amp/sul in 1:1, 2:1, 3:1, 4:1, and 8:1 combinations and pen/sul in 3:1 and 4:1 combinations; six patients in study 72-1 were treated with pen/sul.

TABLE 13c
SERIOUS ADVERSE EXPERIENCES OTHER THAN DEATH
ALL AMP/SUL AND ALL COMPARATIVE AGENTS
NON-U.S. STUDIES WITH >50% PEDIATRIC PATIENTS

Serious Adverse Experiences	Non-U.S. Studies All Amp/Sul		Non-U.S. Studies Comparative Agents	
	N	(%)	N	(%)
Total Number of Patients Treated with Amp/Sul (2:1 Combination only)	1649	100	175	100
Total Number of Patients with Serious Adverse Experiences During Treatment*	10	<1	2	1
Study: SBT/AMP-NY-83-005, Scholz (Amp/Sul 2:1 combination only) Adverse Experience: Paroxysmal event	1	<1	0	-
Study: 88-2, United Kingdom (Amp/Sul 2:1 combination only Comparative agent: Met/Cef) Adverse Experiences:				
Wound Infection	3	<1	0	-
Abdominal and wound pain	1	<1	0	-
Abdominal pain	0	-	1	<1
Abscess	1	<1	0	-
Vomiting and gastroenteritis	0	-	1	<1
Study: SBT/AMP-TW-86-003, Taiwan (Amp/Sul 2:1 combination) Adverse Experience: Hemolytic anemia	1	<1	0	-
Study 72-1, Greece (Pen/Sul) Adverse Experience: Elevated transaminases	1	<1	0	-
Study SBT/AMP-EED-87-001, Czechoslovakia (Amp/Sul 2:1 combination) Adverse Experience Thoracic Tumor	1	<1	0	-
Publication: *Riv. Inf. Ped.*, Suppl. 2: p.s28. 1991 by Mantero, et. al. (Amp/sul 2:1 combination only) Adverse Experience: Worsening of lymphadenitis requiring surgery	1	<1	0	-

* With the exception of the two patients (12 years of age) in Study 88-2, all patients were children <12 years of age.

Medical Officer's Comments: One death occurred in a Unasyn-treated pediatric patient in the non-U.S. studies. The rate of serious adverse events appears similar for Unasyn-treated patients compared to comparative-agent treated patients [10/1649 (0.6%) patients vs 2/175 (1.1%) patients]. A summary of the serious adverse events in Unasyn-treated vs comparative agent-treated patients follows:

SERIOUS ADVERSE EVENTS BY TREATMENT REGIMEN FOR INTENT TO TREAT PATIENTS

	Treatment Regimen	
	Unasyn (N=1649)	Comparative Agent (N=175)
Serious Adverse Event	N (%)	N (%)
Death	1 (<1%)[1]	0 (0%)
Seizures (Paroxysms)	1 (<1%)[2]	0 (0%)
Wound infection	3 (<1%)	0 (0%)
Abscess	1 (<1%)[3]	0 (0%)
Abdominal/wound pain	1 (<1%)	1 (<1%)
Vomiting	0 (0%)	1 (<1%)
Hemolytic anemia	1 (<1%)[4]	0 (0%)
Elevated transaminases	1 (<1%)	0 (0%)
Worsening of lymphadenitis	1 (<1%)[5]	0 (0%)
Thoracic tumor	1 (<1%)[6]	0 (0%)

[1] This patient from Study SBT/AMP-TR-86-002, reported to have died secondary to disseminated intravascular coagulation, was admitted with a diagnosis of fulminant meningococcemia and purpura. The death was considered by the investigator to be unrelated to Unasyn treatment.

[2] This patient from Study SBT/AMP-NY-83-005, Berlin, Germany/Patient [redacted], was admitted with bronchpneumonia and renal failure, hepatomegaly, elevated transaminases, myocarditis, encephalitis and coagulopathy. On day three of Unasyn therapy, the patient developed drowsiness and seizures (paroxysms). The adverse event was considered by the investigator to be related to the severity of underlying illness, and was not considered drug-related.

[3] It is interesting to note four infectious complications of intra-abdominal infections in Unasyn-treated patients (3 wound infections and 1 abscess) compared to no infectious complications in comparative agent-treated patients (metranidazole/cefotaxime).

[4] This patient from Study SBT/AMP-TW-86-003, developed hemolytic anemia while being treated with Unasyn for pneumococcal pneumonia. Direct and indirect Coombs tests were negative. The investigator felt this adverse event was possibly related to study drug and the patient's condition resolved sucessfully after a blood transfusion and discontinuation of Unasyn. When the applicant reviewed the adverse events database for Unasyn, another five cases of possible hemolytic anemia in adults which may have been associated with use of Unasyn administration were identified.

[5] This patient would additionally be considered a Unasyn treatment failure.

[6] The applicant provided no further information pertaining to this patient.

Medical Officer's Comments: The rates of serious events in Unasyn-treated and comparative agent-treated patients are small. The one patient death and one

episode of seizures seem unlikely to be related to Unasyn administration. Several treatment failures for Unasyn used in therapy of intra-abdominal infections are reported, but the information provided is too scant to be used to argue that an increased rate of infectious complications in Unasyn-treated vs. comparative agent-treated patients might exist. The adverse event of hemolytic anemia possibly related to Unasyn is concerning, particularly in light of the five reported adult patients with hemolytic anemia. The current Unasyn package insert list agranulocytosis and positive Coombs test as adverse reactions under the *Hematologic* section. This portion of the label may need to be amended to include the adverse event of hemolytic anemia.

Table 10a (prepared by the applicant) presents the incidence and severity of adverse events experienced by Unasyn-treated patients:

TABLE 10a
INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES (ALL CAUSALITIES)
ALL NON-US STUDIES WITH >50% PEDIATRIC PATIENTS*
ALL AMP/SUL

Adverse Experiences	Patient Incidence All Amp/Sul* N (%)	Severity Mild	Moderate	Severe	Unknown
Total No. of Patients Evaluated#	1628 (100)				
No. of Patients With Adverse Experiences	88 (5)				
No. of Patients Discontinued Due to Adverse Experiences	9 (<1)				
Total No. Adverse Experiences	96	29	35	3	29
Adverse Experiences					
Diarrhea	24 (1)	11	12	0	1
Pain at the injection/infusion site	20 (1)	2	4	0	14
Loose and/or soft stools**	12 (<1)	8	3	0	1
Rash**	11 (<1)	2	5	0	4
Vomiting**	6 (<1)	2	3	0	1
Urticaria	6 (<1)	1	4	1	0
Exanthema	3 (<1)	2	1	0	0
Nausea	2 (<1)	0	1	0	1
Fever	2 (<1)	0	1	0	1
Changes in alvus (G.I.)	1 (<1)	0	0	0	1
Clostridium difficile	1 (<1)	0	0	0	1
Encephalitis	1 (<1)	0	0	0	1
Erythema	1 (<1)	1	0	0	0
Gastroenteritis	1 (<1)	0	0	0	1
Hemolytic anemia	1 (<1)	0	0	1	0
Myocarditis	1 (<1)	0	0	0	1
Paroxysmal event	1 (<1)	0	0	1	0
Relapse *Candidiasis*	1 (<1)	0	0	0	1
Thrombophlebitis	1 (<1)	0	1	0	0

* Includes amp/sul in 1:1, 2:1, 3:1, 4:1, and 8:1 combinations and pen/sul in 3:1 and 4:1 combinations; six patients in study 72-1 treated with pen/sul.

\# Included are patients in 48/49 studies with safety data available. In study SBT/AMP-NY-87-003, Fanta, no adverse experience data were available.

** Seven incidences of loose stools (SBT/AMP-STM-B-87-002), one incidence of vomiting (SBT/AMP-STM-B-87-002), and one incidence of maculopapular rash occurred on oral sultamicillin therapy (*Riv. Inf. Ped.*, Suppl. 2:p. s28-s33).

Medical Officer's Comments: As in the previously reviewed U.S. studies, the most common adverse events associated with Unasyn administration are related to the gastrointestinal and skin and skin structure systems. A substantial number of adverse events in non-U.S.Unasyn-treated patients were related to pain at the injection/infusion site. This finding may be related to the significantly larger number of patients treated with Unasyn by IM administration in non-U.S. patients (538/1649 (33%) vs 3/154 (1.9%), p=0.00000001).

Table 12a (prepared by the applicant) presents the incidence of discontinuations from protocol due to adverse events in Unasyn-treated patients in non-U.S. studies with >50% pediatric patients:

TABLE 12a
PREMATURE DISCONTINUATIONS DUE TO ADVERSE EXPERIENCES
NON-US STUDIES WITH >50% PEDIATRIC PATIENTS
ALL AMP/SUL

Discontinuations Due to Adverse Experiences	All Amp/Sul#	
	(N)	(%)
Total No. of Patients Treated	1649	100
No. Patients Discontinued Due to Adverse Experiences##	9	<1
Adverse Experiences Which Led to Discontinuation:		
Urticaria	3	<1
Rash	2	<1
Fever & rash	1	<1
Relapse *Candidiasis*	1	<1
Thrombophlebitis	1	<1
Urticaria & diarrhea	1	<1

\# Includes amp/sul in 1:1, 2:1, 3:1, 4:1, and 8:1 combinations and pen/sul in 3:1 and 4:1 combinations; six patients in study 72-1 were treated with pen/sul.

Two patients >12 years of age were discontinued for the following adverse experiences: relapse *Candidiasis* and thrombophlebitis.

Medical Officer's Comments: The rate of discontinuation from protocol due to adverse events in Unasyn-treated patients was 9/1649 (<1%). This reflects no increased rate of discontinuations for adverse events when compared to U.S. Unasyn-treated pediatric patients. The types of adverse events prompting discontinuation are also similar for non-U.S. Unasyn-treated pediatric patients when compared to U.S. Unasyn-treated pediatric patients.

Table 16a (prepared by the applicant) presents the rate of laboratory test abnormalities among patients treated with Unasyn:

TABLE 16a
INCIDENCE OF STUDY DRUG RELATED LABORATORY ABNORMALITIES
AMONG PATIENTS TREATED WITH AMP/SUL
NON-US STUDIES WITH >50% PEDIATRIC PATIENTS

Laboratory Abnormalities Possibly Related to Study Drug	**All Amp/Sul***	
	(N)	(%)
Total No. of Patients Evaluated*	1270**	100
No. of Patients w/Laboratory Abnormalities	125	10
No. Patients w/Hematology Abnormalities#	68	5
Hematology Parameters:		
Elevated		
Eosinophils	43	3
Platelets	17	1
Decreased		
Hematocrit	3	<1
Hemoglobin	3	<1
WBC	2	<1
Granulocytes	2	<1
Platelets	1	<1
RBC	1	<1
No. Patients w/Serum Chemistry Abnormalities#	62	5
Serum Chemistry Parameters:		
Increased		
SGOT	27	2
SGPT & SGOT	18	1
SGPT	9	1
Transaminase	6	<1
LDH	4	<1
Bilirubin***	2	<1
Alkaline Phosphatase	2	<1
No. Patients w/Coagulation Abnormalities#	5	<1
Coagulation parameters:		
Increased		
Prothrombin time	1	<1
Positive PIVKA	1	<1
Positive PIVKA II	1	<1
Decreased		
Quick's value	2	<1

* Includes amp/sul in 1:1, 2:1, 3:1, 4:1, and 8:1 combinations and pen/sul in 3:1 and 4:1 combinations; six patients in study 72-1 treated with pen/sul.

** Denominator denotes either the number of patients in a study or the number of patients who had a particular laboratory test performed. Therefore, this number does not reflect the total number of amp/sul patients. Total number of patients analyzed for any laboratory parameter was 1270. For hematology the total number of patients analyzed was 1268, for coagulation the total number of patients analyzed was 1231, and for serum chemistry the total number of patients analyzed was 1262. The incidence of abnormalities is calculated for each category.

\# Some patients may have had more than one laboratory abnormality.

*** Includes total and direct bilirubin.

Medical Officer' Comments: Among the non-U.S. pediatric patients treated with Unasyn, approximately 10% had possibly treatment-related laboratory test abnormalities. In this population, abnormal values most frequently reported were: eosinophils, platelets, SGOT, and SGPT. Laboratory abnormalities are similar to those reported in the three U.S. studies previously reviewed.

Medical Officer's Final Comments on Safety Review of Non-U.S. Studies:

The rate of serious adverse events, including death, for both Unasyn- and comparative agent-treated patients is small for non-U.S. studies in pediatric patients, although this may be in part attributed to differences in adverse reporting rates between the U.S. and other countries. Similarly, the rates of "non-serious" adverse events associated with Unasyn administration are small, and occur predominantly in the gastrointestinal and skin and skin structure systems (similar to the distribution seen for adverse events in the U.S. Unasyn-treated pediatric population). The rate of laboratory abnormalities possibly related to Unasyn administration was 10% in non-U.S. studies with >50% pediatric patients. The most common laboratory abnormalities occurred in eosinophils, platelets, SGOT, and SGPT; similar abnormalities were noted in the U.S. pediatric studies.

IV. SUMMARY RECOMMENDATIONS

The Medical Officer recommends that ampicillin/sulbactam (Unasyn) be approved for the treatment indication of skin and skin structure infections (SSTI) in pediatric patients under the recently promulgated "Pediatric Rule" (21 CFR Part 201 "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule", December 13, 1994). The results of the clinical efficacy study and safety analyses are supportive of the efficacy and safety of Unasyn in pediatric patients above one year of age, when used at a dose of 300 mg per kg per day (up to maximum of 40 kg), administered in equally divided doses every 6 hours via the intravenous route, for the treatment of SSTI. More specific labeling guidance will be provided in the labeling review.

This concludes the review of NDA 50-608, Supplement Number SE5-019.

Susan A. Maloney, M.D., M.H.S.
Reviewing Medical Officer
Division of Anti-Infective Drug Products

cc: Original NDA 50-608
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/SMaloney
HFD-520/Pharm/HSun
HFD-520/Micro/PDionne
HFD-520/Chem/SRoy
HFD-520/CSO/Debellas

Concurrence Only:
HFD-520/DivDir/MFanning MF 2/16/96
HFD-520/SMO/RRoberts KR 1/25/96

APPENDIX A: SKIN AND SKIN STRUCTURE INFECTIONS (SSTI): DIFFERENCES IN EVALUABILITY BETWEEN APPLICANT AND MEDICAL OFFICER

APPENDIX A: SSTI: Differences in Evaluability between Applicant and Medical Officer

Patient No.	Drug	Applicant	Reason	Officer	Reason
	U[1]	noneval[2]	NBP[3]	CE-failure[4]	fever, surg>48[5]
	U	noneval	NBP	noneval	prior abx[6]
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	no F/U[7]
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	success		noneval	no F/U
	U	success		noneval	no F/U
	U	success		noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	CE-success	
	U	noneval	minimum[8]	noneval	inapp dx[9]
	U	noneval	NBP	noneval	prior abx
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	concurrent abx[10]
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	minimum
	U	noneval	NBP	CE-success	

[1]U=Unasyn,[2]noneval=not evaluable,[3]NBP=no baseline pathogen, [4]CE=Clinical evaluation, [5]surg>48=surgery at >48 hours,[6]prior abx=prior antibiotics,[7]no F/U=no follow-up,[8]minimum=< than minimum therapy,[9]inapp dx=inappropriate diagnosis, [10]concurrent abx=concurrent antibiotics[11]C=cefuroxime, [12]inapp dose=inappropriate dose

APPENDIX A: (CONT.)

Patient No.	Drug	Applicant	Reason	Officer	Reason
	U	noneval	NBP	noneval	inapp dx
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	CE-success	
	U	success		noneval	prior abx
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	prior abx
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	concurrent abx
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	CE-failure	surg>48
	U	noneval	NBP	CE-failure	symptoms
	U	noneval	NBP	noneval	prior abx
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	prior abx
	U	success		noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	minimum	noneval	inapp dx

[1]U=Unasyn,[2]noneval=not evaluable,[3]NBP=no baseline pathogen, [4]CE=Clinical evaluation, [5]surg>48=surgery at >48 hours,[6]prior abx=prior antibiotics,[7]no F/U=no follow-up,[8]minimum=< than minimum therapy,[9]inapp dx=inappropriate diagnosis, [10]concurrent abx=concurrent antibiotics[11]C=cefuroxime, [12]inapp dose=inappropriate dose

APPENDIX A: (CONT.)

Patient No.	Drug	Applicant	Reason	Officer	Reason
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	success		noneval	no F/U
	C[11]	success		noneval	no F/U
	C	noneval	NBP	noneval	no F/U
	C	noneval	NBP	noneval	prior abx
	C	noneval	NBP	noneval	no F/U
	C	noneval	NBP	CE-success	
	C	success		noneval	no F/U
	C	noneval	inapp dx	noneval	no F/U
	C	noneval	inapp dose[12]	noneval	prior abx
	C	noneval	NBP	noneval	prior abx
	C	noneval	NBP	noneval	concurrent abx
	C	success		noneval	no F/U
	C	success		noneval	prior abx
	C	success		noneval	no F/U
	C	noneval	NBP	noneval	prior abx
	C	success		noneval	no F/U
	C	noneval	NBP	CE-failure	symptoms
	C	success		noneval	no F/U
	C	noneval	NBP	noneval	no F/U
	C	success		noneval	no F/U
	C	success		noneval	no F/U
	C	noneval	NBP	noneval	no F/U
	C	success		noneval	no F/U
	C	success		noneval	no F/U
	C	success		noneval	no F/U
	C	success		noneval	prior abx

[1]U=Unasyn,[2]noneval=not evaluable,[3]NBP=no baseline pathogen, [4]CE=Clinical evaluation, [5]surg>48=surgery at >48 hours,[6]prior abx=prior antibiotics,[7]no F/U=no follow-up,[8]minimum=< than minimum therapy,[9]inapp dx=inappropriate diagnosis, [10]concurrent abx=concurrent antibiotics[11]C=cefuroxime, [12]inapp dose=inappropriate dose

APPENDIX A: (CONT.)

Patient No.	Drug	Applicant	Reason	Officer	Reason
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	CE-success	
	C	noneval	NBP	CE-success	
	U	noneval	minimum	noneval	prior abx
	U	noneval	NBP	CE-success	
	U	success		noneval	prior abx
	U	noneval	NBP	CE-failure	symptoms
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	success		noneval	prior abx
	U	noneval	inapp dx	CE-failure	surg>48
	C	noneval	NBP	noneval	no F/U
	C	noneval	NBP	CE-success	
	C	noneval	NBP	noneval	no F/U
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	prior abx
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	minimum
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	no F/U
	C	noneval	NBP	CE-failure	surg>48
	C	noneval	NBP	CE-success	
	C	noneval	NBP	noneval	FB[13]
	C	noneval	NBP	CE-success	
	U	noneval	NBP	CE-failure	symptoms
	U	success		noneval	prior abx

[1]U=Unasyn,[2]noneval=not evaluable,[3]NBP=no baseline pathogen, [4]CE=Clinical evaluation, [5]surg>48=surgery at >48 hours,[6]prior abx=prior antibiotics,[7]no F/U=no follow-up,[8]minimum=< than minimum therapy,[9]inapp dx=inappropriate diagnosis, [10]concurrent abx=concurrent antibiotics[11]C=cefuroxime, [12]inapp dose=inappropriate dose,[13]FB=foreign body

APPENDIX A: (CONT.)

Patient No.	Drug	Applicant	Reason	Officer	Reason
	U	noneval	NBP	CE-success	
	U	success		noneval	prior abx
	U	success		noneval	prior abx
	U	noneval	NBP	noneval	no F/U
	U	noneval	NBP	CE-failure	symptoms
	U	noneval	NBP	CE-success	
	U	success		noneval	no F/U
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	success		noneval	prior abx
	U	noneval	NBP	noneval	prior abx
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	no F/U
	C	success		noneval	no F/U
	C	noneval	NBP	CE-failure	symptoms
	C	noneval	NBP	noneval	prior abx
	C	noneval	NBP	CE-success	
	C	noneval	NBP	CE-success	
	C	noneval	NBP	CE-success	
	C	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-failure	surg>48
	U	noneval	NBP	noneval	no F/U
	C	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	success		CE-failure	surg>48
	C	success		noneval	prior abx
	U	noneval	inapp dx	noneval	no F/U
	U	noneval	NBP	noneval	no F/U

[1]U=Unasyn,[2]noneval=not evaluable,[3]NBP=no baseline pathogen, [4]CE=Clinical evaluation, [5]surg>48=surgery at >48 hours,[6]prior abx=prior antibiotics,[7]no F/U=no follow-up,[8]minimum=< than minimum therapy,[9]inapp dx=inappropriate diagnosis, [10]concurrent abx=concurrent antibiotics[11]C=cefuroxime, [12]inapp dose=inappropriate dose,[13]FB=foreign body

APPENDIX A: (CONT.)

Patient No.	Drug	Applicant	Reason	Officer	Reason
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	U	success		noneval	no F/U
	U	noneval	NBP	noneval	no F/U
	C	noneval	NBP	CE-success	
	C	noneval	NBP	noneval	no F/U
	C	noneval	NBP	noneval	no F/U
	C	success		noneval	no F/U
	C	noneval	NBP	CE-success	
	C	noneval	NBP	CE-success	
	C	noneval	NBP	noneval	no F/U
	C	noneval	NBP	noneval	no F/u
	U	noneval	NBP	noneval	prior abx
	U	success		noneval	no F/U
	C	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	noneval	NBP	CE-success	
	U	noneval	NBP	noneval	inapp dx
	U	success		noneval	>14 days[14]
	U	success		noneval	>14 days
	U	success		noneval	>14 days
	C	success		noneval	>14 days

[1]U=Unasyn,[2]noneval=not evaluable,[3]NBP=no baseline pathogen, [4]CE=Clinical evaluation, [5]surg>48=surgery at >48 hours,[6]prior abx=prior antibiotics,[7]no F/U=no follow-up,[8]minimum=< than minimum therapy,[9]inapp dx=inappropriate diagnosis, [10]concurrent abx=concurrent antibiotics[11]C=cefuroxime, [12]inapp dose=inappropriate dose,[13]FB=foreign body, [14]>14 days=> 14 days oral (transitional) therapy

Pages 132-135
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Not Approved
Indication

APPENDIX C: TABLE 1: LISTING OF STUDIES (NON-U.S.)

CLINICAL REPORTS: >50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
SBT/AMP-F-87-001	Begue	France	open comparative		150 tid/qid IV	Cefotaxime 50-100 tid/qid	40	22	18	3 to 15 days
SBT/AMP-I-88-009	Longo	Italy	open comparative		150 bid IM	Ceftazidime 50 bid	60	38	22	5 to 12 days
SBT/AMP-MX-85-02	Santos	Mexico	open comparative		75 bid/tid IV/IM	Cefuroxime 100-150	50	21	29	4 to 28 days
Study 88-2	Morris	United Kingdom	open comparative		22.5 to 90 qid IV	Metronidazole 7.5-22.5 tid; Cefotaxime 25-75 tid	100	57	43	1-3 days
Study 72-1[1]	Syriopoulou	Greece	open non-comparative		150 qid IV[2]	None	27	13	14	2 to 11 days

[1] Filed to original NDA 50-608, Vol. 1.12, Pg. 1866.

[2] Ratios other than 2:1 for ampicillin/sulbactam are utilized.

CLINICAL REPORTS: >50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
Study 89-1[1]	Johansson	Sweden	open non-comparative		300 tid IV	None	4[2]	1	3	2 to 3 days
Study 92-1	Gilly	France	open non-comparative		150 tid IV	None	6[2]	2	4	1 to 11 days
Study 93-1	Reinert	France	open non-comparative		108 to 328.5 qid IV	None	18[3]	4	14	1 to 2 days
SBT/AMP-NY-83-005	Astruc	France	open non-comparative		36 to 225 tid/qid IV	None	41	21	20	3 to 12 days
SBT/AMP-NY-83-005	Bassetti	Italy	open non-comparative		93 to 170 bid/tid/qid IV/IM	None	30	9	21	3 to 8 days

[1] Filed to original NDA 50-608, Vol. 1.13, Pg. 2176.

[2] Two patients also received oral sultamicillin after receiving parenteral amp/sul.

[3] Fifteen patients received oral sultamicillin after receiving parenteral amp/sul.

CLINICAL REPORTS: >50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
SBT/AMP-NY-83-005	Burgio	Italy	open non-comparative		70 to 169 tid IV/IM	None	30	18	12	4 to 10 days
SBT/AMP-NY-83-005	Cedrato	Argentina	open non-comparative		150 tid/qid IM/IV	None	50	26	24	3 to 14 days
SBT/AMP-NY-83-005	Scholz	Germany	open non-comparative		150 tid IV	None	45	28	17	4 to 16.5 days
SBT/AMP-TR-86-002	Kanra	Turkey	open non-comparative		300 to 600 tid/qid IV[1]	None	125	72	53	4 to 44 days
SBT/AMP-PHI-86-003a	Lopez	Philippines	open non-comparative		90 to 230 tid/qid IV	None	43	25	18	7 to 10 days

[1] Ratios other than 2:1 for ampicillin/sulbactam are utilized.

CLINICAL REPORTS: >50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
SBT/AMP-TW-86-003	Lee	Taiwan	open non-comparative		75 to 450 qid IV[1]	None	88	56	32	3 to 30 days
SBT/AMP-TW-86-008	Hwang	Taiwan	open non-comparative		75 to 200 qid IV	None	21	14	7	3 to 14 days
SBT/AMP-PAK-87-001	Isani	Pakistan	open non-comparative		750 to 3000 mg/day qid IV	None	25	10	15	3 to 13 days
SBT/AMP-F-88-001	Relier	France	open non-comparative		150 to 225 bid/tid IV	None	10[2]	5	4	5 to 11 days

[1] Ratios other than 2:1 for ampicillin/sulbactum are utilized.

[2] The sex of one patient was not available.

CLINICAL REPORTS: >50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
SBT/AMP, STM-B-87-002	Gęubelle	Belgium	open non-comparative		42 to 363 tid/qid IV/IM	None	41[1]	28	13	1 to 4 days
SBT/AMP-EED-87-001	Strachunsky	CIS	open non-comparative		150 tid/qid IM/IV	None	103	58	45	5 to 21 days
SBT/AMP-EED-87-001	Cervenka	Czecho-slovakia	open non-comparative		150 qid IV/IM	None	18	--	--	3 to 14 days
SBT/AMP-EED-87-001	Kreska	Poland	open non-comparative		150 IV	None	24	1	23	10 days
SBT/AMP-NY-87-003	Fanta	Chile	open non-comparative		150 bid IM	None	21	--	--	7 days

[1] Thirty-eight patients received oral sultamicillin after receiving parenteral amp/sul.

CLINICAL REPORTS: >50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
SBT/AMP-NY-87-001	Vergara	Chile	open non-comparative		150 qid IV	None	40	22	18	8 to 14 days
Study 64-1[1]	Cockburn	United Kingdom	open non-comparative		60[2] and 100[2] bid IV	None	16	7	9	1 to 4 days

[1] Filed to original NDA 50-608, Vol. 1.8, Pg. 497.

[2] Ratios other than 2:1 for ampicillin/sulbactam are utilized

PUBLICATIONS: >50% PEDIATRIC PATIENTS

Journal Article	Author	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
J. Korean Pediatric Assoc. 29(1)	Lee, Khang, et. al.	Korea	open comparative		150 tid/qid IV/IM	Ampicillin 100 qid; Amikacin 15-20 bid	100	60	40	4 to 12 days
Jap. J Antib. XLII(3): 598-611	Iwata, Yamada, et. al.	Japan	open non-comparative		60 to 316 tid/qid IV	None	63	35	28	2 to 14 days
Jap. J Antib. XLII(3): 612-622	Meguro, Arimasu, et. al.	Japan	open non-comparative		80 to 308 tid/qid IV	None	33	20	13	3 to 12 days
Jap. J Antib. XLII(3): 623-638	Sato, Narita, et. al.	Japan	open non-comparative		54 to 150 tid/qid IV	None	34	27	7	3 to 12 days
Jap. J Antib. XLII(3): 639-650	Nakao, Kimura, et. al.	Japan	open non-comparative		79 to 154 tid/qid IV	None	23	15	8	4 to 11 days

PUBLICATIONS: >50% PEDIATRIC PATIENTS

Journal Article	Author	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
Jap. J Antib. XLII(3): 651-661	Ito, Ihara, et. al.	Japan	open non-comparative		90 to 500 tid/qid IV	None	25	13	12	17 days
Jap. J Antib. XLII(3): 662-674	Nakamura, Miyazu, et. al.	Japan	open non-comparative		92 to 220 tid/qid IV	None	36	17	19	3 to 7 days
Jap. J Antib. XLII(3): 675-685	Ito, Mayumi, et. al.	Japan	open non-comparative		88 to 133 tid/qid IV	None	24	9	15	4 to 11 days
Jap. J Antib. XLII(3): 687-700	Nishimura, Tabuki, et. al.	Japan	open non-comparative		60 to 300 tid/qid IV	None	25	12	13	3 to 8 days
Jap. J Antib. XLII(3): 701-717	Hattori, Higashino, et. al.	Japan	open non-comparative		76 to 200 tid/qid IV	None	24	13	11	2 to 12 days
Jap. J Antib. XLII(3): 719-724	Haruta, Kuroki, et. al.	Japan	open non-comparative		94 to 190 tid/qid IV	None	20	16	4	3 to 10 days

PUBLICATIONS: >50%. PEDIATRIC PATIENTS

Journal Article	Author	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
Jap. J Antib. XLII(3): 725-731	Takeda, Hosoda, et. al.	Japan	open non-comparative		83 to 167 tid IV	None	18	15	3	4 to 21 days
Jap. J Antib. XLII(3): 733-742	Sekiguchi, Okamoto, et. al.	Japan	open non-comparative		62.5 to 413.8 tid/qid IV	None	20	10	10	4 to 22 days
Jap. J Antib. XLII(3): 743-753	Hayashi, Kida, et. al.	Japan	open non-comparative		100 to 145 qid IV	None	21	12	9	3 to 10 days
Jap. J Antib. XLII(3): 754-765	Yanagishima Yanai, et. al.	Japan	open non-comparative		100 to 312.5 tid/qid IV	None	24	12	12	4 to 14 days
Jap. J Antib. XLII(3): 766-772	Ogura, Hisakawa, et. al.	Japan	open non-comparative		100 to 300 tid/qid IV	None	9	5	4	4 to 17 days
Jap. J Antib. XLII(3): 773-790	Motohiro, Sakata, et. al.	Japan	open non-comparative		30 to 180 tid/qid IV	None	65	32	33	3 to 23 days

PUBLICATIONS: >50% PEDIATRIC PATIENTS

Journal Article	Author	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
Jap. J Antib. XLII(3): 579-593	Sato, Ishikawa, et. al.	Japan	phase I		26 to 267 qid IV	None	30	--	--	1 to 14 days
Riv. Inf. Ped., 5 (1): 33-36	Tornaghi, Massironi, et. al.	Italy	open non-comparative		75 bid IV/IM	None	30	15	15	4 days minimum
Riv. Inf. Ped., Suppl. 2: 28-33	Mantero, Perata, et. al.	Italy	open non-comparative		150 bid/tid IM/IV	None	28[1]	12	16	2 to 4 days
Riv. Inf. Ped., Suppl. 2: 34-40	Pavesio, Pecco, et. al.	Italy	open non-comparative		150 bid IM	None	29	20	9	5 to 9 days
Rev. Chil. de Inf. 6 (2): 72-75	Siri, Ledermann, et. al.	Chile	open non-comparative		100 qid IV	None	30	--	--	7 days

[1] Twenty-eight patients received oral sultamicillin after receiving parenteral amp/sul.

PUBLICATIONS: >50% PEDIATRIC PATIENTS

Journal Article	Author	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
Osp. Ital. Pediatr. 23: 534-542	DiGruttola, Schiavulli, et. al.	Italy	open non-comparative		150[1] bid/tid IV/IM	None	37	18	19	5 to 30 days

[1] Ratios other than 2:1 for ampicillin/sulbactam are utilized.

CLINICAL REPORTS AND PUBLICATIONS: ≤50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
Study 52-2[1]	Mehtar	United Kingdom	Open non-comparative		3 to 6 g qid IV/IM	None	23	14	9	3 to 10 days
Minerva Medica 82 (6): 387-394	Chiodo, Manfredi, et. al.	Italy	open comparative		150 to 225 IV/IM	Mezlocillin 75 to 200	65	37	28	4 to 20 days
SBT/AMP-STM-B-87-004	Verdonk	Belgium	open non-comparative		4.5 g IV	None	40	--	--	5 to 19 days
SBT/AMP-COL-88-001	Villanueva	Columbia	open non-comparative		0.075 to 12 g tid/qid IV/IM	None	50	--	--	7 days
SBT/AMP-COL-89-001	Multicenter Study	Columbia	open non-comparative		0.6 to 3.5 g tid/qid IV	None	34	8	--	3 to 15 days

[1]Filed to original NDA 50-608, Vol. 1.12, Pg. 1690.

CLINICAL REPORTS AND PUBLICATIONS: ≤50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
SBT/AMP-COL-89-002	Multicenter Study	Columbia	open non-comparative		150 tid/qid IV/IM	None	61	--	1	24 hrs
SBT/AMP-EED-87-001	Perepanova	CIS	open non-comparative		1.5 to 6.0 g tid/qid IV/IM	None	33	--	--	7 to 10 days
SBT/AMP-EED-87-001	Utkin	Latvia	open non-comparative		3.0 to 12.0 g bid/tid/qid IV/IM	None	30	--	--	6 to 14 days
Infection Magazine 2(2): 205-214	Ege and Can	Izmir	open non-comparative		100 bid IV/IM	None	37	4	2	7 days
SBT/AMP-TR-89-001	Alparslan	Turkey	open non-comparative		1.5 g bid IV 50 bid po	None	20	2	2	14 to 32 days 10 to 28 days

CLINICAL REPORTS AND PUBLICATIONS: ≤50% PEDIATRIC PATIENTS

Protocol Number	Principal Investigators	Location	Study Design	Age Range	Unasyn Daily Dose Range, mg/kg	Control Agent, Daily Dose mg/kg	Total # of Patients	M	F	Duration of Unasyn Treatment
STM-VEN-89-004	Multicenter Study	Venezuela	open non-comparative		N/A IV/IM	None	170	--	--	N/A
Curr. Ther. Res. 41: 128	Dutse	Nigeria	open non-comparative		6 g qid IM	None	60	3	3	5 days

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Ongoing Studies

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 050608

STATISTICAL REVIEW

Statistical Review and Evaluation
(Addendum)

NDA: NDA 50-608/SE5-019

Applicant: Pfizer Inc.

Name of Drug: Unasyn (ampicillin sodium/sulbactam sodium)

Indication:

Type of Report: Clinical Report

Clinical Input: Susan Maloney, M.D. (HFD-520)

In my original statistical review dated 11/22/94, the analyses of the sponsor's evaluable data sets showed that ampicillin/sulbactam and Cefuroxime and ampicillin/sulbactam and ampicillin/clindamycin with an aminoglycoside are not statistically different for Skin and Skin Structure Infections respectively, in the treatment of pediatric patients, relative to bacteriologic and clinical responses.

The reviewing medical officer (RMO) differed from the sponsor in determining evaluability of patients and in assessing clinical outcomes. The results of the analyses of the reviewing medical officer's data sets (ITT and Evaluable) and that of the sponsor's are the same for the indication, Skin and Skin Structure Infections. But, for the indication, the medical officer's data sets (ITT and Evaluable) showed that the 95% confidence intervals for the difference (ampicillin/sulbactam- ampicillin/clindamycin with aminoglcoside) do not satisfy the DAIDP guidelines for therapeutic equivalence of two drugs (Evaluable: $_{50,22}(-0.305,0.087)_{80\%,91\%}$ for clinical outcome at the end of study protocol; ITT: $_{131,64}(-0.154,0.019)_{88.5\%,95.3\%}$ for the clinical outcome). The results of the clinical and bacteriological outcomes in Evaluable Patients (MO's data set) by treatment regimen for Visit 1 (10-14 days after study drug discontinuation), Visit 2 (4-6 weeks after study drug discontinuation) and Overall (at least one follow-up visit) also support the above findings at the end of study protocol [Visit 1: $_{47,21}(-0.324,0.089)_{78.7\%,90.5\%}$, Visit 2: $_{46,20}(-0.331,0.096)_{78.3\%,90.0\%}$, and Overall: $_{50,22}(-0.305,0.087)_{80.0\%,90.9\%}$].

Thus, based on reviewing medical officer's evaluability criteria and assessment of clinical responses, it is concluded that ampicillin/sulbactam ***does not fulfill the regulatory definition of therapeutic equivalence*** in the treatment of in ***pediatric patients.***

12/13/'95

R. Srinivasan, Ph.D
Acting Team Leader, Biometrics IV

Concur: Ralph Harkins, Ph.D 12/13/95
Acting Division Director, Biometrics IV

cc:
Archival NDA 50608/SE5-019

HFD-520
HFD-520/Mr. Debellas
HFD-520/Dr. Roberts
HFD-520/Dr. Maloney
HFD-520/Dr. Fanning
HFD-701/Dr. Anello
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-344/Dr. Thomas

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This addendum contains 2 pages

Srinivasan/December 14, '95/Z4594/WP Text Windows 6.1/C:\reviews.nda\Unasyn.add

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 050608

MICROBIOLOGY REVIEW

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Microbiological Review of Efficacy Supplement

NDA #: 50-608 **REVIEW #:** 1 **REVIEW DATE:** 09-NOV-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT	30-NOV-93	01-DEC-93	11-OCT-95

NAME & ADDRESS OF APPLICANT:

PFIZER INC.
235 East 42nd Street
New York, NY 10017-5755

CONTACT PERSON:
Robert B. Clark
Phone Number: (212) 573-3412

DRUG PRODUCT NAME:

Proprietary:	Unasyn
Nonproprietary:	ampicillin sodium/sulbactam sodium
Chemical Type:	penicillin antibiotic/β-lactamase inhibitor
Therapeutic Class:	3 C

ANDA Suitability Petition/DESI/Patent Status:
U.S. patent 4,234,579; expires November 18, 1999

PHARMACOLOGICAL CATEGORY/INDICATION:
penicillin antibiotic/β-lactamase inhibitor/treatment of skin and skin structure infections caused by susceptible pathogens.

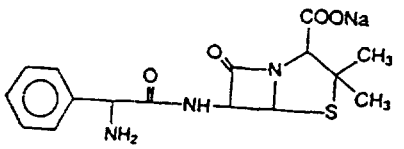
DOSAGE FORM:	Parenteral
STRENGTHS:	1.5 g; 3 g
ROUTE OF ADMINISTRATION:	Intravenous or Intramuscular
DISPENSED:	_X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL AND MOLECULAR FORMULA, MOL.WT:

AMPICILLIN SODIUM:

Chemical Name: (2S,5R,6R)-6-[(R)-2-Amino)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, monosodium

Chemical Structure:

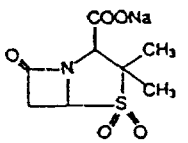


Molecular Formula: $C_{16}H_{18}N_3O_4SNa$
Molecular Weight: 371.39

SULBACTAM SODIUM:

Chemical Name: (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide, monosodium

Chemical Structure:



Molecular Formula: $C_8H_{10}NO_5SNaO$
Molecular Weight: 255.22

SUPPORTING DOCUMENTS:

IND:

CONCLUSIONS & RECOMMENDATIONS:

This application is APPROVABLE from an overall microbiology perspective. However, final labeling will need to be negotiated. The sponsor should be sent the comments listed on pages 47 to 55 of this review.

Pages 3-4
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INTRODUCTION

This supplemental application has been submitted for the purpose of extending use of Unasyn to pediatric patients) for two of the indications (not gynecological infections) as currently approved for adults. The currently approved indications for adults are the treatment of skin and skin structure infections, intra-abdominal infections and gynecological infections. The application contains neonatal toxicology data, pharmacokinetic data, two U.S. multicenter studies (one per indication) and other supportive studies.

The annotated package insert included with the submission makes no changes to the 'Microbiology' subsection. The label is old, however, and does not conform to present labeling. The organisms listed are all in one listing and are not separated into those with clinical efficacy and those with only *in vitro* activity. Susceptibility testing methods also need to be undated.

The sponsor states that pathogens which cause skin and skin structure infections in children are generally the same as those in adults, except that *Haemophilus influenzae* are more frequently isolated in children. Bacteria commonly isolated from children hospitalized with skin infections include *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenzae,* and Bite wounds often result in infections caused by a mixture of aerobic and anaerobic flora including and *Bacteroides fragilis*. All of these organisms, except are listed in the present label. *Haemophilus influenzae* is the only organism in the above list that produces β-lactamases that is not listed in the Indications and Usage section. This is probably due to the fact that it is not commonly found in adult infections.

Adults and children usually have the same organisms causing infections. Aerobes most frequently isolated are *Escherichia coli,* enterococci, *Klebsiella, Proteus,* and *Enterobacter* species. Streptococci, staphylococci, and *Pseudomonas* (ampicillin/sulbactam resistant) are also isolated. Anaerobic bacteria include *Bacteroides. Clostridium,* and anaerobic cocci. All of these organisms are in the microbiology labeling.

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

The mechanism of action of ampicillin/sulbactam in a 2:1 combination was demonstrated in NDA 50-608. No new data are submitted in this supplementary submission.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The current label for UNASYN (ampicillin/sulbactam) has indications for the following organisms: *Staphylococcus aureus, Acinetobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Proteus mirabilis,* and *Bacteroides fragilis.* Although the current label has only one list for all organisms, the following organisms are listed in the present label, but are not included in the indications section so they would now be included in the *in vitro*/no clinical efficacy only listing: *Enterococcus faecalis, Staphylococcus epidermidis, Staphylococcus saprophyticus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Haemophilus influenzae, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Proteus vulgaris, Providencia rettgeri,* and *Providencia stuartii.*

The following organisms are included in the Indications and Usage section for ampicillin alone and would, therefore, also be susceptible to the combination product: staphylococci, streptococci including *Streptococcus pneumoniae*, enterococci, non-penicillinase producing *Haemophilus influenzae,* non-penicillinase producing *Neisseria gonorrhoeae, Escherichia coli,* and *Proteus mirabilis.*

Although the January, 1993, NDA holders' letter had been issued at the time that this supplement was submitted, this supplement was not submitted to update the 'Microbiology' subsection to conform to this letter. Recent literature was, therefore, not submitted in order to retain organisms in the *in vitro* only list in the package insert. The sponsor has submitted a number of recent (at least from the submission date of the supplement in November, 1993) studies on the *in vitro* activity of ampicillin/sulbactam, however, and since the NDA holders' letter had been issued when this supplement was submitted this literature will be used to update the label.

GRAM-POSITIVE AEROBES

ENTEROCOCCUS FAECALIS

TABLE 1

Activity of ampicillin/sulbactam against *Enterococcus faecalis*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Jones (1)	USA	25	NCCLS microdilution	1988	0.5	0.5

Only one study has been included and only 25 isolates have been tested. The MIC_{90} value is well below the susceptible breakpoint of ≤ 8 μg/mL. This organism is also in the Indications and Usage section of the ampicillin package insert. Since this organism is in the indications section of the ampicillin label it should be allowed to be in the combination product label even though less than 100 isolates were tested and only one study was performed. This study indicates that the organism is susceptible.

STAPHYLOCOCCUS AUREUS

TABLE 2

Activity of ampicillin/sulbactam against *Staphylococcus aureus*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Aldridge (2)	USA	20 $Meth^R$	MHB microdilution	1986	–	32
Tally (3)	USA	33	NCCLS broth dilution	1983	–	8
Kulhanjian(4)	USA	31	NCCLS broth dilution	1989	0.78	1.56
Retsema (5)	USA	70 Amp^R	NCCLS broth dilution	1986	2	4
		75 $Meth^R$			16	16
Jones (1)	USA	32 β-lac +	NCCLS broth dilution	1988	1	2
		18 β-lac -			0.12	0.12
		10 $Meth^R$			1	1
Barry (6)	USA	174 $Meth^R$	NCCLS broth dilution	1990	16	>32
		71 $Meth^S$			2	4
Neu (7)	Spain	20	NCCLS agar dilution	1989	0.5	2
		20 $Meth^R$			4	8

A large number of USA isolates were tested. The MIC_{90} values for all isolates except the methicillin-resistant isolates were ≤8 μg/mL, which is the susceptible breakpoint. The MIC_{90} values for the methicillin-resistant isolates were often above this breakpoint. *Staphylococcus aureus* may remain in the label, but methicillin-resistant strains will be considered as being resistant to ampicillin/sulbactam. This organism is included in the Indications and Usage section for ampicillin/sulbactam.

STAPHYLOCOCCUS EPIDERMIDIS

TABLE 3

Activity of ampicillin/sulbactam against *Staphylococcus epidermidis*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Aldridge (2)	USA	20 $Meth^R$	MHB microdilution	1986	–	32
Tally (3)	USA	19	NCCLS broth dilution	1983	–	8
Retsema (5)	USA	25	NCCLS broth dilution	1986	≤1	4
Jones (1)	USA	14 β-lac +	NCCLS broth dilution	1988	1	8
		10 β-lac -			0.12	2
Barry (6)	USA	120 $Meth^R$	NCCLS broth dilution	1990	8	16
		44 $Meth^S$			4	8

Over 100 USA isolates, excluding the methicillin-resistant isolates, were tested. The MIC_{90} values for all isolates except the methicillin-resistant isolates were ≤8 μg/mL, which is the susceptible breakpoint. The MIC_{90} values for the methicillin-resistant isolates were often above this breakpoint. *Staphylococcus epidermidis* may remain in the label, but methicillin-resistant strains will be considered as being resistant to ampicillin/sulbactam.

STREPTOCOCCUS PYOGENS

TABLE 5

Activity of ampicillin/sulbactam against *Streptococcus pyogens*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Kulhanjian(4)	USA	14	NCCLS broth dilution	1989	≤0.01	≤0.10
Jones (1)	USA	21	NCCLS broth dilution	1988	0.03	0.03

Although only 35 isolates were tested the MIC_{90} values in both studies were below the ≤ 0.12 μg/mL susceptible breakpoint for ampicillin which is used for ampicillin/sulbactam testing of streptococci. This organism is in the current label. This organism is also included in the ampicillin label in the Indications and Usage section under *Infections of the respiratory tract* and since ampicillin alone is indicated for the organism, ampicillin-sulbactam should be at least equally as good against it. *Streptococcus pyogens* may remain in the label.

STREPTOCOCCUS PNEUMONIAE

TABLE 6

Activity of ampicillin/sulbactam against *Streptococcus pneumoniae*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Kulhanjian(4)	USA	3	NCCLS broth dilution	1989	≤0.10	≤0.10
Jorgensen (8)	USA	468 Pen-S	NCCLS broth dilution	1990	0.03	0.03
		18 Pen-I			0.12	0.5
Jones (1)	USA	26	NCCLS broth dilution	1988	0.06	0.25

This organism is included in the indications section of the ampicillin only label. Well over 100 isolates were tested. The MIC_{90} value is above the susceptible breakpoint for penicillin of 0.06 μg/mL in studies that did not separate the penicillin-susceptible isolates from the intermediate and resistant ones. Ampicillin has no separate breakpoints and penicillin breakpoints are to be used. Since this organism is included in the Indications section of the ampicillin label, it should also remain in the ampicillin/sulbactam label.

SUMMARY OF GRAM-POSITIVE ACTIVITY

The following gram-positive organisms may be included in the package insert. Other organisms may be included in the section of organisms that ampicillin/sulbactam has been shown to have clinical efficacy for if the clinical picture reveals that they should be listed. Conversely, if the clinical picture reveals that some of the genera/species that are susceptible by *in vitro* methods are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.

Gram-positive aerobes

Enterococcus faecalis
Staphylococcus aureus (β-lactamase and non-β-lactamase producing)
Staphylococcus epidermidis (β-lactamase and non-β-lactamase producing)
Streptococcus pneumoniae
Streptococcus pyogenes

The following gram-positive organisms that are in the present labeling should be removed unless the Medical Officer determines that ampicillin/sulbactam has clinical efficacy against them:

Staphylococcus saprophyticus--no data have been submitted in this submission for this organism.
Streptococcus agalactiae--only data from one study with 22 isolates were submitted (this organims is not in the present label).
Streptococcus viridans--only data for two isolates were submitted.

GRAM-NEGATIVE AEROBES

ACINTOBACTER SPECIES

TABLE 7

Activity of ampicillin/sulbactam against *Acinetobacter* species

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Kulhanjian (4)	USA	1	NCCLS broth	1989	3.12	---
Retsema (5)	USA	20	NCCLS broth	1986	1.6	3.1
Jones (1)	USA	20	NCCLS broth	1988	1	1

This genus is included in the Indications and Usage section for ampicillin/sulbactam and, therefore, must stay in the label. The MIC_{90} values in all studies is below the susceptible breakpoint of ≤ 8 μg/mL.

ENTEROBACTER SPECIES

TABLE 9

Activity of ampicillin/sulbactam against *Enterobacter* species

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Tally (3)	USA	24	NCCLS broth	1983	–	128
Retsema (5)	USA	14 *aerogenes*	NCCLS broth	1986	8	16
Jones (4)	USA	20 *aerogenes*	NCCLS broth	1988	8	>16
Jones (4)	USA	20 *agglomerans*	NCCLS agar	1988	2	4
Retsema (5)	USA	28 *cloacae*	NCCLS broth	1986	64	>128
Jones (4)	USA	20 *cloacae*	NCCLS broth	1986	2	16

This genus is included in the Indications and Usage section of the label for ampicillin/sulbactam and must, therefore, remain in the label. Most studies had MIC_{90} values greater than the $\leq$ 8 μg/mL NCCLS breakpoint.

ESCHERICHIA COLI

TABLE 10

Activity of ampicillin/sulbactam against *Escherichia coli*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Retsema (5)	USA	150	NCCLS broth	1986	2	16
Tally (3)	USA	75	NCCLS broth	1983	–	32
Shungu (9)	USA	62	NCCLS agar	1989	2	32
Aldridge (2)	USA	20	MHB microdilution	1986	–	128
Jones (1)	USA	30	NCCLS broth	1988	2	16
Gill (10)	USA	293	NCCLS agar	1991	2	32
Gaterman (11)	GER	55 TEM-1	NCCLS agar dilution	1991	8	512
		25 OXA-1			16	32
		74 chromosomal			16	64

This organism is included in the Indications and Usage section for ampicillin/sulbactam and, therefore, must stay in the label. The MIC_{90} values in all studies are greater than the susceptible breakpoint of ≤ 8 μg/mL.

HAEMOPHILUS INFLUENZAE

TABLE 11

Activity of ampicillin/sulbactam against *Haemophilus influenzae*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Mortensen (12)	USA 5 centers	494	NCCLS-HTM broth dilution	1990	–	1.0
Azimi (13)	USA	45 β-lac+	Supplemented MHB broth	1989	0.39	0.78
		30 β-lac -			≤0.2	0.39
Kulhanjian (4)	USA	3 β-lac+	NCCLS-broth	1989	0.78	0.78
		5 β-lac -			0.39	0.39
Jones (1)	USA	30 Amp^S	NCCLS broth microdilution	1988	0.12	0.25
		31 Amp^R			0.5	1.0
Aldridge (2)	USA	20	MHB-broth	1986	–	2.0
Retsema (5)	USA	20 Amp^R	BHI broth	1986	0.5	2.0

All studies produced an MIC_{90} value of ≤2.0 μg/mL, which is the susceptible breakpoint. A large number of isolates were tested in a number of studies throughout the United States. *Haemophilus influenzae* may remain in the label.

KLEBSIELLA SPECIES

TABLE 12

Activity of ampicillin/sulbactam against *Klebsiella* species

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Tally (3)	USA	56	NCCLS broth	1983	–	64
Jones (1)	USA	40	NCCLS broth	1988	4	16
Gill (10)	USA	160	NCCLS agar	1991	4	32
Retsema (5)	USA	18 *oxytoca*	NCCLS broth	1986	16	16
Retsema (5)	USA	42 *pneumoniae*	NCCLS broth	1986	8	8
Shungu (9)	USA	40 *pneumoniae*	NCCLS agar	1989	4	32

This genus is included in the Indications and Usage section of the label for ampicillin/sulbactam and must, therefore, remain in the label. Most studies had MIC_{90} values greater than the ≤ 8 μg/mL susceptible breakpoint.

NEISSERIA GONORRHOEAE

TABLE 15

Activity of ampicillin/sulbactam against *Neisseria gonorrhoeae*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{100}
Kulhanjian (4)	USA	1	NCCLS	1989	≤0.10	–
Retsema (5)	USA	12	BHI broth	1986	0.31	2.5

This organism is in the Indications and Usage section of the ampicillin label and, therefore, will be allowed in the label for the combination product. Very few isolates were tested in this submission. The MIC_{100} value in one study was 2.5 μg/mL. Only β-lactamase testing is recommended for this organism.

PASTEURELLA MULTOCIDA

TABLE 16

Activity of ampicillin/sulbactam against *Pasteurella multocida*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Goldstein (14)	USA	20	NCCLS broth	1988	0.125	0.25
Girard (15)	USA	41	BHI broth	1987	$\leq$ 0.10	0.20

Sixty-one isolates were tested in two studies. The MIC_{90} values were very low in both studies. *Pasteurella multocida* may cause wound infections after an animal bite. *Pasteurella multocida* may be added to the package insert.

PROTEUS MIRABILIS

TABLE 17

Activity of ampicillin/sulbactam against *Proteus mirabilis*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Retsema (5)	USA	23	NCCLS broth	1986	2	8
Jones (1)	USA	30	NCCLS broth	1988	0.5	1
Gaterman (11)	GER	29 TEM-2	NCCLS agar	1991	32	1024

This organism is included in the Indications and Usage section of the ampicillin/sulbactam label so it will remain in the label. The MIC_{90} value was equal to or less than the $\leq$ 8 μg/mL NCCLS breakpoint for all studies except for the Gaterman study which included only isolates with a TEM-2 plasmid. It appears that the combination product does not extend ampicillin's spectrum to this organism if it contains this plasmid.

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SUMMARY OF GRAM-NEGATIVE ACTIVITY

The following gram-negative organisms may be included in the package insert. Other organisms may be included in the section of organisms that ampicillin/sulbactam has been shown to have clinical efficacy if the clinical picture reveals that they should be listed. Conversely, if the clinical picture reveals that some of the genera/species that are susceptible by *in vitro* methods are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.

Gram-negative aerobes

Acintobacter calcoaceticus
Enterobacter species (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical efficacy has been demonstrated)
Escherichia coli (Although most strains of *Escherichia coli* are resistant *in vitro*, clinical efficacy has been demonstrated)
Haemophilus influenzae (β-lactamase and non-β-lactamase producing)
Klebsiella species (Although most strains of *Klebsiella* species are resistant *in vitro*, clinical efficacy has been demonstrated)
Neisseria gonorrhoeae (β-lactamase and non-β-lactamase producing)
Pasteurella multocida
Proteus mirabilis

The following gram-negative organisms that are in the present labeling should be removed unless the Medical Officer determined that ampicillin/sulbactam has clinical efficacy against them:

ANAEROBES

BACTEROIDES FRAGILIS

TABLE 21

Activity of ampicillin/sulbactam against *Bacteroides fragilis*

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Retsema (5)	USA	26	BHI agar dilution	1986	0.8	1.6
Tally (7)	USA	71	NCCLS agar dilution	1983	–	8
Aldridge (2)	USA	20	Anaerobic broth	1986	–	4
Leone (16)	Italy	196	NCCLS agar dilution	1990	1	8
Wexler (17)	USA	77	Brucella laked agar dilution	1991	2	4
Neu (7)	USA	20	Brucella laked agar dilution	1989	0.15	0.25

The MIC_{90} values in all studies were ≤ 8 μg/mL, which is the susceptible breakpoint for anaerobic testing. Well over 100 isolates were tested from a number of different locations. This organism is also in the Indications and Usage section of the product label. *Bacteroides fragilis* may remain in the label.

BACTEROIDES FRAGILIS GROUP

TABLE 22

Activity of ampicillin/sulbactam against *Bacteroides fragilis* group

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Wexler (18)	USA	70	Brucella laked agar dilution	1985	2	8
Jones (1)	USA	63	NCCLS broth dilution	1988	1	2
Cornick (19)	USA 7 centers	506	BHI agar dilution	1990	0.25	0.5
Applebaum (20)	USA	217 β-lac +	NCCLS agar dilution	1991	–	16
Cuchural (21)	USA 7 centers	534	BHI agar dilution	1991	0.25	2
Retsema (5)	USA	24 *thetaiotaomicron*	BHI agar dilution	1986	1.6	3.1
Leone (16)	Italy	23 *thetaiotaomicron*	NCCLS agar dilution	1990	0.5	2
Retsema (5)	USA	17 *vulgatis*	BHI agar dilution	1986	1.6	6.3
Leone (16)	Italy	6 *vulgatis*	NCCLS agar dilution	1990	2	8
Wexler (17)	USA	90	Brucella laked agar dilution	1991	2	16

The MIC_{90} values in all studies were ≤ 8 μg/mL, which is the susceptible breakpoint for anaerobic testing. Well over 100 isolates were tested from a number of different locations. *Bacteroides fragilis* group may be placed in the label.

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CLOSTRIDIUM SPECIES
TABLE 24
Activity of ampicillin/sulbactam against *Clostridium* species

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Wexler (18)	USA	33	Brucella laked agar dilution	1985	0.5	2
Leone (16)	Italy	26	NCCLS agar dilution	1990	0.5	2
Wexler (18)	USA	10 *difficle*	Brucella laked agar dilution	1985	2	4
Leone (16)	Italy	10 *difficle*	NCCLS agar dilution	1990	0.125	1
Wexler (17)	USA	25 *difficle*	Brucella laked agar dilution	1991	2	4
Leone (16)	Italy	82 *perfrigens*	NCCLS agar dilution	1990	0.25	0.5
Wexler (17)	USA	27 *perfrigens*	Brucella laked agar dilution	1991	0.25	0.5

The MIC_{90} values in all studies were ≤ 8 μg/mL, which is the susceptible breakpoint for anaerobic testing. Over 100 isolates were tested from a number of different studies. *Clostridium species* may remain in the label.

PEPTOSTREPTOCOCCUS SPECIES

TABLE 25

Activity of ampicillin/sulbactam against *Peptostreptococcus* species

Investigator	Country	# Tested	Method	Year Published	MIC_{50}	MIC_{90}
Wexler (18)	USA	36	Brucella laked agar dilution	1985	0.25	0.5
Leone (16)	Italy	7 *magnus*	NCCLS agar dilution	1983	0.25	0.5
		9 *asaccharolyticus*			0.25	2
		13 *anaerobius*			0.125	0.5
Wexler (17)	USA	30	Brucella laked agar dilution	1991	0.25	1
Goldstein (14)	USA	10	NCCLS agar dilution	1988	0.06	0.5

The MIC_{90} values in all studies were $\leq$ 8 μg/mL, which is the susceptible breakpoint for anaerobic testing. Seventy-six isolates were from USA studies and another 29 were from Italy. Although less than 100 USA isolates were tested the MIC_{90} values are low enough to allow this genius to remain in the label with less than 100 isolates being tested in the USA.

SUMMARY OF ANAEROBIC ACTIVITY

The following anaerobic organisms may be included in the package insert. Other organisms may be included in the section of organisms that ampicillin/sulbactam has been shown to have clinical efficacy for if the clinical picture reveals that they should be listed. Conversely, if the clinical picture reveals that some of the genera/species that are susceptible by *in vitro* methods are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.

Anaerobic Bacteria

Bacteroides fragilis
Bacteroides fragilis group
Clostridium species
Peptostreptococcus species

The following anaerobic organisms that are in the present labeling should be removed unless the clinical picture reveals that ampicillin/sulbactam has clinical efficacy against them:

MECHANISMS OF RESISTANCE STUDIES

This submission includes a few new studies on resistance development. Neu et al (7) used serial broth dilution containing mixtures of β-lactamase positive and negative organisms in two-fold increasing concentrations of ampicillin and ampicillin/sulbactam. Organisms were removed from the tube with the highest concentration of antibiotic showing growth and transferred daily for 5-8 days. Over 7 days, the ampicillin MIC for an inoculum of mixed β-lactamase-negative and β-lactamase positive *Staphylococcus aureus* rose from μg/mL; the ampicillin/sulbactam MIC for this inoculum rose from μg/mL. Over 8 days, the ampicillin MIC for a mixed inoculum of β-lactamase-negative *S. aureus* and β-lactamase positive *S. epidermidis* rose from μg/mL; the ampicillin/sulbactam MIC for this inoculum remained at 1/1μg/mL. Sulbactam was also shown in this study to inhibit β-lactamases from in *S. aureus, S. epidermidis,* and *Bacteroides fragilis*.

Jacoby and Carreras (22) introduced plasmids into *E. coli* C600 for susceptibility testing. The MICs for a variety of drugs including ampicillin alone and in combination with sulbactam were determined by agar dilution. Sulbactam was best in extending susceptibility to ampicillin (MIC of ≤ 8μg/mL) against strains producing TEM-3, TEM-4, TEM-7, TEM-9, CAZ-2, and SHV-5. It was least effective (MIC of ≥ 256 μg/mL) against TEM-2, SHV-1, SHV-2, SHV-3 and SHV-4.

These experiments show that ampicillin/sulbactam reduces that rate of mutations to resistance for *Staphylococcus* species that produce β-lactamases. Sulbactam is active against most of the TEM β-lactamases, but not very active against the SHV type enzymes.

PRECLINICAL EFFICACY *(IN VIVO)*

PHARMACOKINETICS/BIOAVAILABILITY

The information in this section is taken from the studies submitted in the supplement and have not been evaluated by a Biopharmaceutical Reviewer at the present time.

After a 15 minute I.V. infusion of 2.0 grams of ampicillin/sulbactam, peak serum concentrations (C_{max}) in adult males ranged from μg/mL for ampicillin and from μg/mL for sulbactam, respectively; mean half-life values were approximately 1 hour for ampicillin and sulbactam. Protein binding of both ampicillin and sulbactam was approximately 38%.

In the present submission, pharmacokinetics were determined in pediatric patients receiving ampicillin/sulbactam doses of 48.7 to 75.0 mg/kg q.i.d.. The range of C_{max} values in pediatric patients receiving a 15 minute infusion was μg/mL for ampicillin and μg/mL for sulbactam. The range of AUC was μg-h/mL for ampicillin and μg-h/mL for sulbactam. One patient exhibited an extremely low volume of distribution and one displayed anomalous pharmacokinetic results due to an error in blood collection. If the values for these two patients are omitted, the C_{max} values range from μg/mL for ampicillin and μg/mL for sulbactam, while AUC values range from μg-h/mL for ampicillin and μg-h/mL for sulbactam.

These pharmacokinetic parameters in pediatric patients given 49 to 75 mg/kg q.i.d. were similar to those in adults given a 2 gram infusion.

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

Several studies published in the medical literature have been presented. Two studies (23,24) examined abscesses in the groin area of mice caused by *Bacteroides fragilis-Escherichia coli.* These studies showed that ampicillin/sulbactam administered subcutaneously was effective in preventing a groin infection in mice caused by *Bacteroides fragilis*, but was ineffective against some β-lactamase producing strains of *E. coli.*

In an experimental *Escherichia coli* infection in mouse thigh ampicillin/sulbactam was not very effective against an ampicillin-resistant strain or a TEM-1 strain (25).

In an experiment of intra-abdominal sepsis in rats (26), a gelatin capsule containing mixed aerobic and anaerobic bacteria was surgically implanted in the pelvic region of rats. One group was given ampicillin/sulbactam 72/36 mg every 6 hours for 7 days and another group served as untreated controls. About half the untreated died and all the surviving controls had abscess formation. All treated rats lived and none had abscess. Ampicillin/sulbactam was a success in this treatment.

Fasching et al (27) studied *Staphylococcus* infections in rabbits. They inserted six extravascular cellulose chambers in the subcutaneous space on the backs of rabbits. The authors studied numerous drugs including ampicillin/sulbactam which was administered intramuscularly four hours after inoculation of the chambers and given every 6 hours for 96 hours. Three animals were given drug and two were untreated controls. Results showed that ampicillin/sulbactam was as effective as vancomycin against staphylococci infections.

Hirano et al (28) studied experimental endocarditis in rabbits caused by β-lactamase producing oxacillin-resistant staphylococci. They showed that ampicillin/sulbactam was more effective than oxacillin and vancomycin, although the infection caused by a strain with high oxacillin-resistance was only successfully treated in slightly more than half the animals.

English et al (29) studied the effectiveness of ampicillin/sulbactam in several animal models. In their experiments, unlike the ones above the ampicillin/sulbactam ratio was 1:1 instead of 2:1. In one experiment a filter-paper disk saturated with an ampicillin-resistant strain of *E. coli* was implanted in the skin of mice. A single dose of test compound was then immediately administered subcutaneously. Ampicillin/sulbactam (50 mg/kg) reduced the bacteria count about 2 logs from the control after 3 days. Ampicillin alone showed no reduction. In another experiment rats were inoculated intranasally with *H. influenzae*. On days 5 and 6 all rats with positive blood cultures were administered a single subcutaneous dose of antibiotic. On day 7, rats were killed and blood and CSF samples were taken. In blood ampicillin/sulbactam (50 mg/kg) reduced the bacterial count from 5.7 log cfu to 1.4 log cfu. Ampicillin alone only reduced the count to

4.7 log cfu. In CSF, ampicillin/sulbactam reduced the count from 5.0 log cfu (control) to 0.9 log cfu, while ampicillin alone only reduced the count to 4.2 log cfu. In a final experiment the authors advanced a polyethylene cannula into the right carotid artery until it reached the left ventricle. Endocarditis was produced by the intravenous inoculation of 10^5 ampicillin-resistant *S. aureus*. Antibiotics were given twice daily for 2 days, starting 24 hours after inoculation. The number of bacteria in log cfu/g vegetation was : controls 8.8; ampicillin 50 mg/kg plus sulbactam 50 mg/kg, <2.0; ampicillin 7.4; sulbactam, 8.3. All these experiments show that ampicillin/sulbactam was effective while ampicillin was not.

Washington et al (30) studied experimental endocarditis in rabbits caused by staphylococci. Approximately 4×10^7 *S. aureus* organisms were injected into an ear vein 6-12 hours after a polyethylene tube was introduced through the right carotid artery into the left ventricle. Three groups of animals were studied: 1) inoculated with *S. aureus* strain 1 (nafcillin-sensitive) and received 72 hours of antibiotic therapy, 2) inoculated with *S. aureus* strains 2 and 3 (both nafcillin-resistant) and received 72 hours of therapy, 3) inoculated with *S. aureus* strain 1 and received 32 hours of therapy. Antibiotic therapy was initiated 8 hours after inoculation. Intravenous antibiotic regimens were given to groups 1 and 2 as follows: ampicillin 100 mg/kg, sulbactam 100 mg/kg, ampicillin/sulbactam 100/100 mg/kg, nafcillin 200 mg/kg; all doses given every 8 hours. In group 3 the doses were ampicillin/sulbactam 200/200 mg/kg every 4 hours, nafcillin 200 mg/kg every 8 hours or nafcillin/gentamicin 200/3.4 mg/kg every 8 hours. Eight hours after the last dose vegetations were cultured. Results of experiment 1, nafcillin-sensitive strain: the number of bacteria were: untreated control (n=6), 9.2 log cfu; ampicillin (n=7), 8.9 log cfu; sulbactam (n=6), 9.0 log cfu, nafcillin (n=6), 0.5 log cfu; and ampicillin/sulbactam (n=7), sterile culture. Experiment 2, nafcillin-resistant strains: the number of bacteria were: untreated control (n=5), 10.2 log cfu; ampicillin (n=3), 9.8 log cfu; sulbactam (n=3), 9.7 log cfu, nafcillin (n=18), 5.7 log cfu; and ampicillin/sulbactam (n=17), 0.9 log cfu. In experiment 3, nafcillin-sensitive strain: the number of bacteria were: untreated control (n=4), 9.3 log cfu; nafcillin (n=6), 1.2 log cfu; nafcillin/gentamicin (n=9), 0.7 log cfu; and ampicillin/sulbactam (n=6), 0.6 log cfu. In each of the three experiments all control animals died, none of the ampicillin/sulbactam treated animals died.

All these experiments show that ampicillin/sulbactam is effective in certain animal model infections caused by *Bacteroides fragilis,* staphylococci, and *Haemophilus influenzae.* The dosing in many of these experiments was also in the range of 49 to 75 mg/kg which is the dose range in this supplement.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

Three clinical trials are presented in this supplemental application.

89CE20-0449 Multicenter, randomized, comparative open-label study comparing ampicillin/sulbactam versus cefuroxime in the treatment of skin and/or skin structure infections in hospitalized pediatric patients.

89CE20-0450 Multicenter, randomized, comparative open-label study comparing ampicillin/sulbactam plus an optional aminoglycoside versus ampicillin plus clindamycin plus an aminoglyoside in the treatment of intra-abdominal infections in hospitalized pediatric patients.

90CE20-0493 Multicenter, non-comparative open label study of ampicillin/sulbactam in the treatment of periorbital/preseptal and facial cellulitis in hospitalized pediatric patients. This study was discontinued due to a decrease in the incidence of the disease and no claim is being pursued.

In study 89CE20-0449 two hundred and thirty-four (234) patients were enrolled. There were 154 patents in the ampicillin/sulbactam group and 80 in the cefuroxime group. Seventy-five (75) in the ampicillin/sulbactam group and 42 in the cefuroxime group completed the study. This required the patient to complete the course of treatment and also return for the end of therapy visit and the 10-14 day post-therapy visit. Patients were between 3 months and 11 years of age. Among these patients 95 (62%) of the ampicillin/sulbactam and 41 (51%) of the cefuroxime patients were excluded from efficacy analyses. The most common reasons for exclusion were: no baseline pathogen (amp/sul, 80 and cefuroxime, 33) and less than minimum therapy (amp/sul, 9 and cefuroxime, 6). Clinical and bacteriological responses were analyzed for all treated patients. Among evaluable patients the dose of amp/sul in a 2:1 combination was 219.8 mg/kg/day administered parenterally in four divided doses for a mean duration of 4.9 days. A bacteriological success (eradication) was defined as the elimination of the probable pathogen(s) as determined by repeat culture or by the absence of appropriate material for culture at follow-up (end of parenteral therapy). The patient bacteriological eradication rate at the end of parenteral therapy was 93% (55/59) in the amp/sul treatment group and 97% (38/39) in the cefuroxime group.

Pathogens found in the skin and/or skin structure study (2 or more isolates):
Staphylococcus aureus--40 of 44 (91%) eradicated
Streptococcus pyogenes--16 or 17 (94%) eradicated
Pasteurella multocida--4 of 4 (100%) eradicated
Staphylococcus species (coagulase negative)--3 of 3 (100%) eradicated
Streptococcus viridans--3 of 3 eradicated
Haemophilus parainfluenzae--3 of 3 eradicated
Pasteurella species--2 of 2 eradicated
Enterobacter cloacae--2 of 2 eradicated
Neisseria species--2 of 2 eradicated.

In protocol 89CE20-0450 a total of 197 patients were enrolled; 133 were randomized to receive ampicillin/sulbactam and 64 to receive ampicillin/clindamycin plus an aminoglycoside. Among these patients, 58 amp/sul and 25 amp/clind were excluded from efficacy analyses. The most common reasons for exclusion were no baseline pathogen and concomitant medication. The mean total daily dose of amp/sul for evaluable patients treated with amp/sul was 193.9 ± 54.9 mg/kg/day administered parenterally in four divided doses for a mean duration of 7.7 days. The patient eradication rate at the end of parenteral therapy was 92% (69/75) in the amp/sul group and 95% (37/39) in the amp/clind group.

Pathogens in the study (isolates seen at least 5 or more times):

Pathogen (frequency ≥5)	End of Parenteral	10-14 days	4-6 weeks
Escherichia coli	60/65 (92%)	52/57 (91%)	48/50 (96%)
Bacteroides fragilis	31/33 (94%)	27/30 (90%)	26/28 (93%)
Pseudomonas aeruginosa	23/24 (96%)	23/24 (96%)	22/22 (100%)
Streptococcus viridans	13/16 (81%)	9/11 (82%)	8/9 (89%)
Streptococcus species	12/13 (92%)	9/10 (90%)	9/9 (100%)
Streptococcus species not A,B,O	8/9 (89%)	8/8 (100%)	8/8 (100%)
Bacteroides species	8/9 (89%)	6/6 (100%)	5/5 (100%)
Peptostreptococcus species	6/7 (86%)	7/7 (100%)	5/5 (100%)
Bacteroides fragilis group	5/6 (83%)	6/6 (100%)	6/6 (100%)
Eikenella corrodens	5/5 (100%)	4/5 (100%)	4/5 (100%)
Bacteroides thetaiotaomicron	5/5 (100%)	4/5 (80%)	4/5 (80%)
Bacteroides ovatus	4/5 (80%)	3/3 (100%)	3/3 (100%)

The pathogens listed above are among the ones listed in the package insert for these two diseases in adults.

DISK CONTENT STUDIES

No new studies were performed. All disk diffusion testing was performed using the standard antibiotic disk containing 10 µg of ampicillin and 10 µg of sulbactam.

MIC BROTH/AGAR DILUTION COMPARISONS

No new studies were performed. NCCLS methods were used.

The current approved label, which was approved in 1986 contains the following MIC interpretive criteria

Organisms	Susceptible	Intermediate	Resistant
Gram-negative enterics and staphylococci	≤8	16	≥32
Haemophilus species	≤2	--	≥4

The following MIC interpretive criteria were used in the clinical trials submitted with this supplemental application. These are also the current NCCLS approved criteria:

Organisms	Susceptible	Intermediate	Resistant
Gram-negative enterics and staphylococci	≤8	16	≥32
Haemophilus	≤2	--	≥4
Enterococci†	≤8	--	≥ 16
Streptococci other than *S. pneumoniae*†	≤0.25	0.5-4	≥8

† The interpretive criteria for ampicillin/sulbactam when testing enterococci and nonenterococcal streptococci should be the same as those for ampicillin. *Streptococcus pneumoniae* should be tested using penicillin and interpreted according to penicillin breakpoints.

MIC/DISK DIFFUSION CORRELATION STUDIES

No new studies were performed. NCCLS breakpoints were used. The following zone diameter interpretive criteria were used:

The current label, approved in 1986 contains the following zone diameter interpretive criteria:

Organisms	Susceptible	Intermediate	Resistant
Gram-negative enterics and staphylococci	≥14	12-13	≤11
Haemophilus	≥20	--	≤19

The following zone diameter interpretive criteria were used in the clinical trials submitted with this supplemental application. These were the NCCLS criteria at the time the studies were performed between 1990 and 1992.

Organisms	Susceptible	Intermediate	Resistant
Gram-negative enterics and staphylococci	≥17	14-16	≤13
Haemophilus	≥20	--	≤19
Enterococci†	≥17	--	≤16
Nonenterococcal streptococci†	≥30	22-29	≤21

† The interpretive criteria for ampicillin/sulbactam when testing enterococci and nonenterococcal streptococci should be the same as those for ampicillin.

Since the time of these studies the interpretive criteria have been revised slightly for the gram-negative enterics and staphylococci and new criteria have been established for streptococci. The following criteria will be included in the new label:

Organisms	Susceptible	Intermediate	Resistant
Gram-negative enterics and staphylococci	≥15	12-14	≤11
Haemophilus	≥20	--	≤19
Enterococci†	≥17	--	≤16
β-hemolytic streptococci†	≥26	19-25	≤18

† The interpretive criteria for ampicillin/sulbactam when testing enterococci and nonenterococcal streptococci should be the same as those for ampicillin. Viridans streptococci should be tested for penicillin susceptibility using an MIC method.

For testing ampicillin/sulbactam against gram-negative enterics and staphylococci the zone diameter interpretive standards used in the studies were different from the new recommended NCCLS criteria. The breakpoints used were more conservative than the present criteria, which are almost identical to those in the current label. The NCCLS criteria will be the ones incorporated into the updated package insert.

QUALITY CONTROL STUDIES (MIC AND DISK DIFFUSION)

No new information has been submitted. The current label list the following quality control organisms and ranges:

	Disks	**Mode MIC (mcg/mL ampicillin/ mcg/mL sulbactam)**
Escherichia coli ATCC 25922	20-24 mm	2/1
Escherichia coli ATCC 35218	13-19 mm	8/4
Staphylococcus aureus ATCC 25923	29-37 mm	0.12/0.06

Current NCCLS quality control criteria will be incorporated into the updated package insert. These new criteria will not use mode MICs, but will use MIC ranges for each organism.

The following quality control criteria will be incorporated into the new package insert.

Microorganism	MIC range (μg/mL)	Zone Diameter (mm)
Escherichia coli ATCC 25922		20-24
Escherichia coli ATCC 35218		13-19
Staphylococcus aureus ATCC 25923		29-37
Haemophilus influenzae ATCC 49247		----

CROSS RESISTANCE/CROSS SUSCEPTIBILITY STUDIES

No new information has been provided.

ANAEROBIC STUDIES

No new information has been provided. Interpretive criteria and quality control strains and ranges are not included in the present label. Since this drug is indicated for *Bacteroides fragilis* this information should be included in the label under a section for anaerobic susceptibility testing. The following interpretive criteria should be included in the label as follows:

MIC (μg/mL)	Interpretation
≤8	Susceptible (S)
16	Intermediate (I)
≥32	Resistant (R)

Quality control strains should give the following ranges:

Microorganism	Agar dilution MIC range (μg/mL)	Broth dilution MIC range (μg/mL)
Bacteroides fragilis ATCC 25285		
Bacteroides thetaiotaomicron ATCC 29741		
Eubacterium lentum ATCC 43055		

HAEMOPHILUS AND *NEISSERIA* STUDIES

No new information provided. *Haemophilus* testing was discussed above. *Neisseria* testing is performed with penicillin disk or powder and interpreted according to penicillin criteria. At the present time all *Neisseria* isolates are susceptible and only rare ampicillin-resistant β-lactamase-negative stains of *Haemophilus* are resistant to the combination product in this submission.

BACTERIOLOGICAL EFFICACY

CORRELATION OF TEST RESULTS WITH OUTCOME

In the skin/skin structure study (89CD20-0449) isolates that appeared two or more times had the following susceptibility to ampicillin/sulbactam:

Staphylococcus aureus--42 susceptible; 4 intermediate--4 bacteriological failures
Streptococcus pyogenes--16 susceptible; 1 missing result--1 bacteriological failure
Pasteuruella multocida--4 susceptible--4 of 4 eradicated
Staphylococcus species (coagulase negative)--2 susceptible; 1 intermediate--all eradicated
Streptococcus viridans--2 susceptible; 1 resistant--3 of 3 eradicated
Haemophilus parainfluenzae-- 3 susceptible--3 of 3 eradicated
Pasteurella species--2 susceptible--2 of 2 eradicated
Enterobacter cloacae--1 susceptible; 1 resistant- 2 of 2 eradicated
Neisseria species--2 missing results; 2 of 2 eradicated.

There were very few resistant isolates and even the resistant isolates were eradicated in most cases.

In the study (89CD20-0450) isolates that appeared five or more times had the following susceptibility to ampicillin/sulbactam:

Pathogen (isolates found 5 or more times)
Escherichia coli--37 susceptible; 11 intermediate; 16 resistant; 1 missing result--60 of 65 eradicated.
Bacteroides fragilis--30 susceptible; 3 missing result--31 of 33 eradicated
Pseudomonas aeruginosa--24 resistant--23 of 24 eradicated (aminoglycoside was used in protocol)
Streptococcus viridans--7 susceptible; 9 missing result--13 of 16 eradicated
Streptococcus species--7 susceptible; 6 missing result--12 of 13 eradicated
Streptococcus species not A,B,O--5 susceptible; 2 intermediate; 2 missing result--8 of 9 eradicated
Bacteroides species--6 susceptible; 3 missing result--8 of 9 eradicated
Peptostreptococcus species--4 susceptible; 3 missing result--6 of 7 eradicated
Bacteroides fragilis group--2 susceptible; 4 missing result--5 of 6 eradicated
Eikenella corrodens--4 susceptible; 1 missing result--5 of 5 eradicated
Bacteroides thetaiotaomicron--4 susceptible; 1 missing result--5 of 5 eradicated
Bacteroides ovatus--4 susceptible; 1 missing result--4 of 5 eradicated

Except for *Escherichia coli* most of the pathogens were susceptible. Even most of the resistant isolates were eradicated. *Pseudomonas aeruginosa* isolates were universally resistant, but an aminoglycoside was used in the protocol so these organisms were eradicated. It appears that the susceptibility criteria are adequate and no reason to change them appears in these studies.

PACKAGE INSERT

Pages 39-42
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The sponsor should be informed of the following revisions that must be made to the 'Microbiology' subsection of the label:

1. should be deleted from the label since no data have been submitted in this submission for this organism.

2. should not be added to the label since data from only one study with 22 isolates were submitted.

3. should be deleted from the label since data for only 2 isolates were submitted.

4. should not be added to the label since the MIC_{90} values in the submitted studies were above the 8 μg/mL susceptible breakpoint.

5. should be deleted from the label since only two studies with 21 isolates total have been submitted in this submission for this organism.

6. should be deleted from the label since only one study with 19 isolates and a high MIC_{90} value has been submitted.

7. should be deleted from the label since only one study with 20 isolates and a high MIC_{90} value has been submitted.

8. should be deleted from the label since only one study with 20 isolates and a high MIC_{90} value has been submitted.

9. should be deleted from the label since only one study with 20 isolates and a high MIC_{90} value has been submitted.

10. should be deleted since the only current species is which is not usually a pathogen. No data were submitted for this organism.

11. The 'Microbiology' subsection of the label should be updated to conform with the way this section is written at the present time. This includes separating the listing of organisms into two list; one with both *in vitro* activity and clinical efficacy and a second list with only *in vitro* activity. To be listed in this second listing, usually 100 isolates from various geographical locations across the United States must be tested by NCCLS methods and the MIC_{90} values from these studies must be equal or less than the susceptible breakpoint for these organisms. These organisms must also be potential pathogens in diseases for which the product has an indication.

    The susceptibility testing section must also be updated to include new breakpoints and quality control organisms.

    The 'Microbiology' subsection should be revised to read as follows:

"**MICROBIOLOGY**"

Pages 49-54
Deleted
Labeling Revisions

DEC 5 1996

NDA 50,608/S-019

DATE of SUBMISSION
October 9, 1996

UNASYN
(Ampicillin sodium/Sulbactam sodium)

SPONSOR: Pfizer
235 East 42nd Street,
New York, NY 10017-5755

TYPE OF SUBMISSION: Labeling Supplement **REVIEWER:** HE SUN, Ph.D.

The following labeling comment was conveyed to the sponsor in an FDA approvable letter dated September 11, 1996:

"2. Please include the AUCt above MIC and Cmax/MIC ratios for the pediatric patients in this section of the labeling."

The sponsor's position is that such ratios will not be added to the Unasyn product label due to (1) only limited data of MIC collected from the skin/skin structure study filed in support of this indication in children is available and (2) it is not known how these ratios correlate with clinical response in Unasyn treated patients.

COMMENT: Although we do not know how AUCt above MIC and Cmax/MIC ratios correlate with clinical response in Unasyn treated patient, these parameters do provide good prediction for clinical efficacy. That is why we commonly expect plasma or tissue concentrations higher than MIC for the indication. However, since the sponsor does not have a meaningful MIC database for the indication, the values calculated using this limited information are not meaningful. Therefore, excluding AUCt above MIC and Cmax/MIC ratios in the labeling is acceptable.

12/5/96

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

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

cc:
NDA 50,608/S-019
HFD-520. (Clinical)
HFD-880. (Pelsor, Sun)
HFD-880. Div. File-NDA 50,608
HFD-870. Drug File (Clarence Bott, PKLN Rm. 13B-31)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 050608

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 50,608	SUBMISSION DATE:
SE5 019	Nov. 30, 1993
SE5 019 BB	April 07, 1994
SE5 019 BM	June 02, 1994

PRODUCT: Unasyn (ampicillin sodium/sulbactam sodium) for injection
SPONSOR: Pfizer Central Research.
Eastern Point Road
Groton, CT 06340

TYPE OF SUBMISSION: Supplements **REVIEWER:** HE SUN, Ph.D.

Clinical Pharmacology and Biopharmaceutics Review

NDA 50,608

I. SYNOPSIS

Pharmacokinetic (PK) data were obtained from 28 pediatric patients participating in the Unasyn U.S. clinical efficacy and safety assessment programs. Additional PK data from 51 patients receiving ampicillin/sulbactam in Japan, and 4 patients from a Swedish PK study were also evaluated. PK parameters, C_{max}, AUC, CL, Vd, $t_{1/2}$, from these pediatric groups were comparable to data obtained from adults receiving the drug. The PK information and dose recommendations for children are described in the drug label.

II. RECOMMENDATION

The applicant's Human Pharmacokinetics Section of NDA 50,608 is acceptable for meeting the reqirments of 21 CFR 320.21 and the Clinical Pharmacology labeling reqirments under 21 CFR 201.57. Overall, the applicant's conclusion about these studies are supported by the results provided. Please convey specific comments and labeling comments to the sponsor.

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III. BACKGROUND

Unasyn (ampicillin sodium/sulbactam sodium) is currently approved for the treatment of patients 12 years of age or greater with intra-abdominal, gynecological, and skin and skin structure infections caused by susceptible strains of indicated organisms. The PK of ampicillin and sulbactam in adult humans following parenteral Unasyn (ampicillin/sulbactam, 2:1) administration is usually best represented by a two-compartment open model. Assessed in young, healthy males, the kinetics of sulbactam and ampicillin are similar. After a 15 min IV infusion of 2.0g ampicillin/1.0 g sulbactam (2:1), mean peak serum concentrations (C_{max}) in 24 adult males were 122 and 59 ug/ml for ampicillin and sulbactam (2.07:1), respectively, while mean AUC values were 123 and 66 ug-h/ml for ampicillin and sulbactam (1.86:1), respectively. Mean disposition half-life values were about 1 hour. AUC values are proportional to dose for both drugs, indicating linear kinetics. Ampicillin and sulbactam both distribute into similar apparent volumes of distribution of about 0.25 L/kg.

Co-administration of sulbactam has essentially no effect on the PK of ampicillin, suggesting that the dose regimen of ampicillin does not need adjustment due to the co-administration of sulbactam. Similarly, ampicillin does not affect the PK of sulbactam.

Both drugs are primarily eliminated by excretion and more than 75% of a parenteral dose is typically recovered in urine. The renal clearances of both sulbactam and ampicillin (approximately 200 ml/min and 250 ml/min, respectively) exceed the normal glomerular filtration rate. As might be expected from the renal clearances, the half-life values of sulbactam and ampicillin are significantly and similarly increased in patients with impairment of renal excretion.

Pediatric PK data from 3 U.S. studies (Protocols #89CE20-0449, #89CE20-0450 and #90CE20-0493) and a summary of 12 published articles describing PK in Japanese pediatric patients were included in submission SE5 019; The sponsor updated protocols #89CE20-0449, #89CE20-0450 with additional 11 pediatric patients who completed the study between May 19, 1992 and May 1, 1993, and submitted on June 02, 1994 as SE5 019 (BM); The sponsor also provided a Swedish study to include PK information on 4 pediatric patients in submission SE5 019 (BB).

IV. DRUG FORMULATION

No new drug formulation was presented in this submission. The original drug formulation was presented in original NDA 50,608.

V. SUMMARY OF STUDIES

1. U.S. Studies (in SE5 019 and 019(BM))

PK was assessed in total of 28 pediatric patients (17 from the 1st period and 11 from the 2nd period) aged from less than 1 year to 12 years participating in 3 controlled clinical trials of Unasyn. Three protocols differed principally with regard to the treatment indication. Five blood samples were collected over the course of a dosing interval of 1 or more days after the first dose, and 3 additional samples were collected from as many patients as would volunteer during a second dosing interval

at least 1 day later. Drug concentrations in serum or plasma were determined by HPLC assay.

The range of C_{max} values in these 3 studies for patients receiving a 15 or 16 minute infusion and a 42 to 76 mg/kg Unasyn dose was 81.7 to 446 ug/ml for ampicillin, and 44.4 to 203 ug/ml for sulbactam. The range of AUCt was 92 to 320 mcg-h/ml for ampicillin, and 52.8 to 166 mcg-h/ml for sulbactam. The terminal half-lives are about 1 hour.

No pharmacokinetic parameter exhibited any difference between age groups or exhibited a trend with respect to age. Half-life values for ampicillin and sulbactam were identical to each other (median of 0.8 h each), to those reported previously for healthy adults and to results in other pediatric studies. Ampicillin concentrations exceeded the AUC for a mean of 4.2 h (or 70% of a 6-hr dosing interval) and the mean C_{max}/MIC ratio was 78. These results are consistent with inhibition of the isolated pathogens.

B. Japanese Studies

Pediatric ampicillin/sulbactam PK data from a total of 51 patients (17 females, 26 males and 8 sex unknown) were drawn from 12 published Japanese articles that reported principally safety and efficacy results. Patients aged from 2.4 months to 17 years. Patients received various doses of Unasyn. Blood samples were collected up to 6.67 hours.

The clearance and half-life values of ampicillin and sulbactam did not indicate any trend with respect to the age, sex of the patient or dosing regimen. Eighty percent or more of the Japanese pediatric patients had ampicillin and sulbactam half-life values that were within +/- 25 % of one hour. 31 of the total 51 Japanese patients received doses of 30 to 50 mg/kg. A comparison of C_{max} and AUC values in this subgroup with parameter values in the subgroup receiving 60 mg/kg over similar infusion times suggests linear kinetics in the dosage range of 30 to 60 mg/kg.

C. Swedish Study (Study 89-1)

Four pediatric patients received Unasyn I.V. injection 8 hourly 2-3 days (mean 2.8 day) followed by sultamicillin (a prodrug double ester yielding sulbactam and ampicillin in a 1:1 ratio) suspension 200 mg t.i.d for 2 and 3 days, respectively, in 2 cases. Satisfactory concentrations of both drugs, in the same ratio as the administered dose, were demonstrated in the serum. These concentrations decreased with similar half-lives (0.8-0.9 hours) which correspond closely to those found in adults.

VI. SPECIFIC COMMENTS

1. The area of concentration-time curve above MIC (AUC_{MIC}) and the time at which the drug concentration maintained above the MIC of *Steph.aureus* or *E.coli* (T_{MIC}) will provide important information about the drug's *in vivo* bactericidal activity. The sponsor is encouraged to compare them across different centers and protocols and describe them in the proposed label. (see comments on Labeling #3).

2. Only 1 U.S. and 3 Japanese pediatric patients were less than 1 year old in all these studies. The 1 U.S. patient's PK was significantly different from other children. It is unsafe to project the results to children less than one year old based on these limited data. (see comments on labeling #2).

VII. COMMENTS ON LABELING

The proposed labeling change is attached at the end of the review.

1. The statement in the proposed label under Clinical Pharmacology is different from data reported. It reads as:

   ...". However, the C_{max} value reported from U.S. studies varies from ug/ml for ampicillin, and ug/ml for sulbactam. The proposed labeling should be consistent with the data reported.

2. In dosage and administration section, a dose of 150 to 300 mg/kg/day is recommended for infants and children However, as stated in Comment #2 above, it is difficult to safely project the PK data to pediatric patients Therefore, it is recommended to change the statement as

3. It is recommended that the sponsor provide the AUC_t above MIC and C_{max}/MIC ratios in the proposed label under Clinical Pharmacology Section.

11/21/95

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

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

cc: NDA 50,608, HFD-520 (Clinical, Fogarty), HFD-880 (Fleischer, Pelsor, Sun), Chron, Drug, HFD-19(FOI), HFD-340(Viswanathan).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 050608

ENVIRONMENTAL ASSESSMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: February 12, 1997

From: James D. Bona, R.Ph., M.P.H.
Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
HFD-520/ODEIV/CDER/FDA

To: NDA 50-608/SE5-019, UNASYN (ampicillin sodium/sulbactam sodium), IM/IV.

Subject: Environmental Assessment

This is in reference to the November 30, 1993, supplemental new drug application (NDA) and the resubmission dated October 9, 1996, for NDA 50-608/SE5-019 for UNASYN (ampicillin sodium/sulbactam sodium), IM/IV.

This serves as a memorandum to the file explaining that an Environmental Assessment was NOT required for this application since the previously approved labeling did not specifically exclude use in the pediatric population for skin and skin structure infections. In addition, it would have been overly prohibitive to require an EA from the firm as required in the 1995 issued CDER MAPP 5015.1, Processing Environmental Assessment Submissions, since the application had been submitted in 1993 prior to the MAPP's issuance.

cc: Original NDA 50-608
HFD-520/Div files
HFD-104/T.Nearing
HFD-520/Trostle
HFD-520/Leissa
HFD-830/E.Sheinin
HFD-350/Sager