

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50760

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

NFB 500/TROSTLE
Public Health Service

NDA 50-760

Food and Drug Administration
Rockville MD 20857

MAY 14 1998

SmithKline Beecham Pharmaceuticals
Attention: Sharon W. Shapowal, R. Ph.
One Franklin Plaza, P.O. Box 7929
Philadelphia, PA 19101-7929

Dear Ms. Shapowal:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Amoxil (amoxicillin) Oral Suspension

Therapeutic Classification: Standard

Date of Application: April 15, 1998

Date of Receipt: April 16, 1998

Our Reference Number: 50-760

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 16, 1998, in accordance with 21 CFR 314.101(a).

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

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

Sincerely yours,

JB 5/14/98

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



SmithKline Beecham
Pharmaceuticals

Regulatory Affairs - U.S.
Anti-Infectives and Biological Therapeutic Areas

DESK COPY

J. Cintron

Amendment to a Pending NDA

NDA 50-760

Amoxil® (amoxicillin) for Oral Suspension

Pediatric q12h dosing

March 23, 1999

Janice Soreth, M.D., Acting Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-520)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Response to FDA List of Chemistry Deficiencies and Comments
24-Month Stability Report
Response to FDA Labeling Questions

Dear Dr. Soreth:

We are writing with regard to our New Drug Application for Amoxil® (amoxicillin) for Oral Suspension, NDA 50-760, submitted April 15, 1998, which provides for a change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in pediatric patients, and to provide for new strength suspensions.

At this time, we are amending the NDA with the complete response to the chemistry deficiencies and comments, as cited in the facsimile transmission of March 4, 1999, sent by Mr. José Cintron. For your convenience, the FDA questions/requests precede our responses and are presented in boldface type. Included as part of the chemistry response are updated immediate container labels for the commercial product, sample product labels and revised prescribing information.

If you have any questions regarding NDA 50-760, please do not hesitate to contact me at (215) 751-6318.

Sincerely,

Deneen R. Stewart, Ph.D.

Regulatory Associate

U.S. Regulatory Affairs

Desk copy: J. Cintron (Project Manager)

A. Yu (Chemistry Reviewer)

H. Sun (Biopharm Reviewer)

000001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
 ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
 Expiration Date: April 30, 2000
 See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER
 NDA 50-760

APPLICANT INFORMATION

NAME OF APPLICANT

SmithKline Beecham Pharmaceuticals

DATE OF SUBMISSION

23 March 1999

TELEPHONE NO. (Include Area Code)

(215) 751-6318

FACSIMILE (FAX) Number (Include Area Code)

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

One Franklin Plaza, P.O. Box 7929
 Philadelphia, PA 19101-7929

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Deneen R. Stewart, Ph.D
 Regulatory Associate, U.S. Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

amoxicillin

PROPRIETARY NAME (trade name) IF ANY

Amoxil®

CHEMICAL/BIOLOGICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM:

Oral Suspension

STRENGTHS:

200mg and 400mg

ROUTE OF ADMINISTRATION:

oral

(PROPOSED) INDICATION(S) FOR USE:

The treatment of infections caused by susceptible strains of designated organisms in the following infections: ear, nose, and throat infections, lower respiratory infections, skin and soft tissue infections, genitourinary tract infections and gonorrhea

APPLICATION INFORMATION

APPLICATION TYPE
 (check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
 Name of Drug
 Holder of Approved Application

TYPE OF SUBMISSION
 (check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

Response to FDA Chemisrty Reviewer

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
 - C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
- 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
- 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
- 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
- 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
- 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
- 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.5 (k) (3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. OTHER (Specify) Response to Chemistry Reviewer's questions received by facsimile

CERTIFICATION

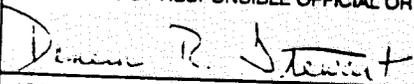
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 315.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Deneen R. Stewart, Ph.D., Regulatory Assoc., U.S. Regulatory Aff.	DATE March 23, 1999
ADDRESS (Street, City, State and ZIP Code) One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101-7929		Telephone Number (215) 751-6318

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 521-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SB
SmithKline Beecham
Pharmaceuticals

73C
ORIGINAL

January 13, 1999

NDA 50-760
Amoxil® (amoxicillin) for Oral Suspension
Pediatric q12h dosing



Gary Chikami, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-520)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Amendment to Pending NDA - 18 Month Stability Report
- Comparative Dissolution data for the '200' and '400' strength suspensions

Dear Dr. Chikami:

Reference is made to our pending New Drug Application for Amoxil® (amoxicillin) Oral Suspension, to allow for a change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in pediatric patients, and to provide for new strength suspensions. The new *Amoxil* suspension (two strengths: 200 mg and 400 mg per 5 mL), is matched in amoxicillin content to the Augmentin® (amoxicillin/clavulanate potassium) suspensions, previously approved for q 12h dosing in pediatric patients.

At this time, in accord with an agreement made between representatives of SmithKline Beecham and the FDA (ref. meeting of January 14, 1997 involving Drs. Katague and Chen, and Mr. Kitz and Ms. Maglennon), we are amending the application to provide an 18-month stability update.

In addition, as agreed between Ms. Maglennon of SB and Dr. Sun [Biopharm] of FDA (ref. telephone conversation of December 10/11, 1998) herein enclosed [Attachments 1 and 2] is dissolution methodology and comparative dissolution data for the '200' and '400' strength suspensions.

Further reference is made to a telephone conversation between Ms. Shapowal [SB] and Dr. Yu [FDA] on December 7, 1998, wherein Dr. Yu asked the following questions:

1. *Please explain the differences between batch B97001 and B97001-AA? And the batch failure associated with B97001-AA?*
2. *Please explain the 6 month timepoint stability failure for one of the batches?*

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N:\amoxil\pedbid\50_760.doc\1

As stated in Volume 1.003, page 000195 of NDA 50-760 submitted April 15, 1998, three Qualification Blends were produced for each strength oral suspension. B97001, B97002, and B97003 for the '200' strength and B97004, B97005 and B97006 for the '400' strength. Each Qualification Blend batch was then filled into a series of different size container closure systems and the size container denoted by a suffix at the end of the Qualification Blend batch number. Below is an example for batch B97001 as detailed on page 000196 of Volume 1.003:

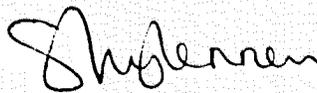
5mL container fill = B97001AA
50mL container fill = B97001B
75mL container fill = B97001C
100mL container fill = B97001D

As detailed on page 000185 of Volume 1.003 B97001AA [i.e. the 5mL container] was filled with material from the first bulk container of Qualification blend B97001 to be discharged into a Binsert [i.e. term used for bulk containers] from the blender. A subsequent investigation revealed that the first Binsert had contained a small amount of poorly blended material. Due to this processing issue, a repeat fill of Qualification blend B97001 [from another Binsert] into 5mL containers was performed and denoted B97001EE. Further, as a result of the investigation, the commercial manufacturing process has been amended as described on page 000270 of Volume 1.003 to prevent this issue arising in the future.

The original NDA included data from evaluation of presentation B97001AA, although it had been replaced by presentation B97001EE. The decision to include B97001AA data in the original NDA was based on the intent to provide complete disclosure of information. However, its presence has caused confusion. We regret that we did not achieve recognition that the B97001AA data should be disregarded and data from B97001EE noted instead. For this reason, data from B97001AA has not been included in this stability update.

Thank you for your kind consideration of the enclosed information. This amendment is being submitted in duplicate. If you have any questions, please do not hesitate to contact me at (610) 917-6457.

Sincerely,



Sharon M. Maglennon
Assistant Director
Regulatory Affairs - North America

cc: Desk Copy - S. Trostle (HFD-520)
S. Shapowal (FP1005)
H. Sun (Biopharm Reviewer)
A. Yu (Chemistry Reviewer)



SmithKline Beecham
Pharmaceuticals

Regulatory Affairs - U.S.
Anti-infectives and Biological Therapeutic Areas

BC

ORIG AMENDMENT

ORIGINAL

Amendment to Pending NDA 50-760
Amoxil® (amoxicillin) for Oral Suspension
q12h dosing

June 19, 1998

Gary Chikami, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-520)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850



Fulfillment of FDA / SB Agreements:
Updated Stability Data
Revision of Debarment Certification

Dear Dr. Chikami:

Reference is made to our pending New Drug Application for Amoxil® (amoxicillin) for Oral Suspension, to allow for a change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in pediatric patients, and to provide for new strength suspensions. The new *Amoxil* suspension (two strengths: 200 mg and 400 mg per 5 mL), is matched in amoxicillin content to the Augmentin® (amoxicillin/clavulanate potassium) suspensions, previously approved for q12h dosing in pediatric patients.

At this time, in accord with an agreement made between representatives of SmithKline Beecham and the FDA (ref. meeting of January 14, 1997 involving Drs. Katague and Chen, and Mr. Kitz and Ms. Maglennon), we are amending the application to provide the 12-month stability report. For the convenience of the chemistry reviewer, the enclosed report takes the form of a total update of Section 7 of the Drug Product section of NDA 50-760 (ref. Volume 1.003, pages 000194-000258), and begins on page 000008 of this submission.

Letter to Dr. Chikami, M.D. Director
June 19, 1998
Page 2

In addition, as agreed between Dr. Pietrusko of SB and Mr. Cintron of FDA (ref. telephone conversation of June 4, 1998), and as submitted by facsimile on June 4th, a revised debarment certification is herein submitted officially to the file. You will find the revised certification on page 000007, below.

This amendment is being submitted in duplicate. If you have any questions, please do not hesitate to contact me at (215) 751-3468.

Sincerely,



Sharon W. Shapowal, R.Ph.
Assistant Director
U.S. Regulatory Affairs

Desk copy: S. Trostle (HFD-520)
A. Dailey (UP-4210)



SmithKline Beecham
Pharmaceuticals

Regulatory Affairs - U.S.
Anti-Infectives and Biological Therapeutic Areas

NDA ~~50-760~~

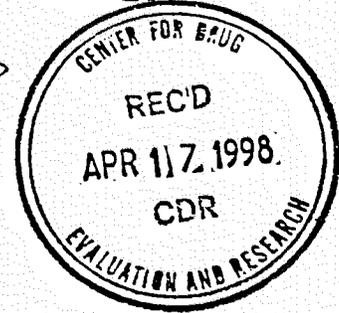
50-760
50542/582403

Amoxil® (amoxicillin) for Oral Suspension
q12h dosing



April 15, 1998

Gary Chikami, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-20)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850



New Drug Application Containing Bioequivalence Data

Dear Dr. Chikami:

Submitted herewith, in duplicate, in accordance with Section 314.0 of Title 21 of the Code of Federal Regulations (21 CFR §314.50) is a New Drug Application for Amoxil® (amoxicillin) for Oral Suspension, to allow for a change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in pediatric patients, and to provide for new strength suspensions. The new *Amoxil* suspension (two strengths: 200 mg and 400 mg per 5 mL), is matched in amoxicillin content to the *Augmentin*® (amoxicillin/clavulanate potassium) suspensions, previously approved for q12h dosing in pediatric patients (Ref. NDA 50-725, approved May 31, 1996).

Substantial evidence of effectiveness of the new *Amoxil* dosage regimens and suspensions was agreed with the Agency to be based upon bioequivalence data in healthy volunteers. For a full recounting of the *Amoxil* q12h development program, please refer to the cover letter and attachments of pending NDA 50-754 (*Amoxil* Tablets for q12h dosing), submitted July 11, 1997. It should be noted that the pivotal bioequivalence protocol to support *Amoxil* suspension and chewable tablets for q12h dosing, and a letter of communication, were submitted to the FDA on July 28, 1997. The pivotal study is entitled: A study to determine the bioequivalence of amoxycillin in novel chewable tablet and suspension formulations of *Amoxil* (400 mg) to the standard marketed formulaiton of *Augmentin* (400/57 mg)", Protocol 2333/057.

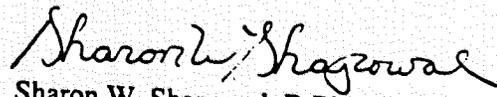
*Letter to Dr. Chikami, M.D. Director
April 15, 1998
Page 2*

Regarding the application user fee, it was agreed between SB and the FDA review team that the sponsor would be required to pay ½ the usual NDA user fee for the previous *Amoxil* Tablet NDA (ref. conversation of March 21, 1997 regarding NDA 50-754). SmithKline Beecham assumes that the new q12h dosing regimen and new strength suspension formulations for pediatric use will require the same fee. The application contains one pivotal bioequivalence study, chemistry, manufacturing and controls data, labeling, and scientific justification/rationale. Pursuant to the Human Prescription Drug User Fee Act of 1992, SB has electronically transferred 100% of the total user fee assessable for 1998. A copy of the User Fee Cover Sheet (Form FDA 3397) is enclosed within this application.

Simultaneously with this submission, an application to allow for new strength chewable tablets (200 mg and 400 mg) for q12h dosing is also being submitted. The data of that application (NDA 50-761) are identical to this application (NDA 50-760) except for chemistry, manufacturing and controls data and immediate container labels specific for the chewable tablets. No user fee monies are submitted for NDA 50-761.

This application is being submitted in duplicate. If you have any questions, please do not hesitate to contact me at (215) 751-3468.

Sincerely,



Sharon W. Shapowal, R.Ph.

Assistant Director

U.S. Regulatory Affairs

Desk copy: Mr. S. Trostle (project manager)