CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-746

CORRESPONDENCE

NDA 50-746

DEC 18 1996

SmithKline Beecham Pharmaceuticals
Attention: Debra Hackett
Manager, U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

Dear Ms. Hackett:

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

Name of Drug Product: Bactroban® (mupirocin calcium cream) Cream, 2%

Therapeutic Classification: Standard

Date of Application: December 12, 1996

Date of Receipt: December 12, 1996

Our Reference Number: 50-746

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act on February 10, 1997 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact Ms. Maureen P. Dillon-Parker, 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,

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

cc:
Original NDA 50-746
HFD-520/Div. Files
HFD-520/PMS/M.Dillon-Parker
HFD-520/CTL/Roberts
HFD-520/CR/Bostwick
DISTRICT OFFICE

drafted: mdp/December 16, 1996/n50746.ack
Final: mdp/December 16, 1996

ACKNOWLEDGEMENT (AC)

SB
SmithKline Beecham
Pharmaceuticals

December 12, 1996

NDA 50-746
Bactroban (mupirocin calcium cream) Cream, 2%
Volumes 1.001 to 1.817

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

New Drug Application

Gentlemen:

Submitted herewith, in duplicate, in accordance with Section 314.50 of Title 21 of the Code of Federal Regulations (21 CFR 314.50) is a New Drug Application (NDA) for the treatment of secondarily infected traumatic skin lesions. Currently, calcium mupirocin cream is available for investigational use under Investigational New Drug Application

The safety and efficacy of Bactroban® (mupirocin calcium cream) Cream for the treatment of secondarily infected traumatic skin lesions was demonstrated in two well-controlled, identical, independent, active-controlled trials (Studies 129A and 129B). In these two double-blind, double-dummy, multicenter trials, patients applied mupirocin calcium cream or placebo cream to the infected lesion under study three times a days for 10 days and took oral cephalexin or oral cephalexin placebo four times daily for 10 days. The proposed labeling is in accordance with the evidence presented in this application to support the marketing of *Bactroban* Cream.

Guidance received and agreements made with members of the Division of Anti-Infective Drug Products during the End of Phase 2 meetings of March 3, 1995 and April 5, 1995, and the pre-NDA meeting of May 14, 1996 have been incorporated into this application. The highlights that follow offer a brief summary of the agreements from the pre-NDA meeting of May 14, 1996.

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400

Preclinical

SB agreed to prepare tabular summaries only of the preclinical data submitted in previously approved applications, NDA 50-591 (Bactroban Ointment) and NDA 50-703 (Bactroban Nasal). These tabular summaries are included in the application and contain cross-referencing to the previous NDA's. Full reports and tabular summaries for all toxicity studies for the cream formulation are submitted in this application. In addition, the toxicology profiles of the two excipients (2-phenoxyethanol and cetomacrogol) are provided in Item 5, Volume 1.010, page 000035 of this application.

Assessment of absorption

Please be advised that additional information is provided to support Study 142. The exact time of urine collection related to the last dose is presented in Table 6.C.1.1 (Volume 1.011, page 000206). In addition, the study summary is available as a part of the CANDA. An ASCII file of the study data is provided for the Biopharmaceutic reviewer (the diskette is provided in Volume 1.001, page 000195 and will be loaded on the network for the reviewer).

Clinical

Based on agreements with the Agency in meetings of March 3, 1995 and April 5, 1995, Clinical trial was amended to become two identical independent trials (Studies 129A and 129B) in order to fulfill the FDA requirement for two adequate and well-controlled studies needed to support the proposed indication for the treatment of treatment of secondarily infected traumatic skin lesions.

At the pre-NDA meeting, it was agreed that SB would expand the protocol specified 7-9 day window for the follow-up visit to 7-12 days. It was also agreed that violation of the "end-of-therapy (EOT)" visit window or missing the EOT visit would not exclude the patient from the per protocol population at follow-up.

Data for this study are submitted in this NDA to support safety only.

CANDA

The CANDA for *Bactroban* Cream will contain the complete review copy of the NDA (Items 1 through 14) and is provided on CD-ROM disks in the archival copy (Volume 1.001, pages 000192 - 000194). The CANDA also will be placed on the Agency's central network server on December 12, 1996 so that the application can be accessed by every reviewer at her/his workstation. This submission is organized according to the format requested in the Form FDA 356h and consists of 817 volumes. Because of the usefulness of this electronic medium, the "paper copy" portion of this NDA consist of 36 volumes only. A printed copy of any portion of the electronic NDA can be easily obtained by printing from the CANDA.

As noted in our pre-NDA meeting of May 14, 1996 and the Agency's subsequent correspondence of September 25, 1996, the Agency agreed to accept a substantial portion of this NDA in an electronic format only. The archival copy of the NDA will consist of a paper copy of the NDA (Items 1 through 14) except for the following items that will be presented to the Agency as electronic files only as either as text searchable and/or electronic images:

- copies of all published literature cited throughout the NDA with the exception of the clinical publications which are provided as a paper copy in Volume 1.035. Publications can be accessed in the CANDA by clicking on the publication PRIM ID number.
- Item 10. Statistical Section: cross-reference to Item 8.
- Item 11. Case Report Tabulations (CRTs): A paper copy of the index to all CRTs is provided in Volume 1.036, page 000002 and also in Volume 1.001, page 000085.
- Item 12. Case Report Forms (CRFs)- all CRFs for studies 129A and 129B with specific notation for withdrawals. CRFs for Study 130 are provided for withdrawals only. There were no deaths reported during or within 30 days after the study, for any cream clinical studies. A paper copy of the index to all CRFs is provided in Volume 1.040, page 000029, and also in Volume 1.001, page 000139.

A paper copy of the CRF tabulations (Volumes 1.036 through 1.039) will be provided to the medical reviewer as a "desk copy."

A "Guide to Reviewers" (located in Volume 1.001, page 000012) provides the organization of the NDA, summarizes the contents of each volume and identifies whether the information is provided in the application as paper copy, electronic images and/or text searchable files.

SAS PHCLIN

To aid the medical and statistical reviewers, we are also providing SAS data within the SAS PHCLIN application which will also be loaded onto the FDA network on December 12, 1996. Training for this application will be scheduled at the reviewers convenience.

Chemistry

In a teleconference of March 8, 1996 between Mr. Peter Kitz (Group Director, SB) and Dr. Suva Roy (Supervisory Chemist), the Agency agreed to the contents of the Qualification batch stability protocol. Dr. Roy also agreed that the initial submission would be sufficient to contain 9 month long term data at 25° C/60% RH and accelerated data at 40° C/75% RH for 6 months and 30° C/60% RH for 9 months.

Debarment Statement

Please be advised that the debarment certification, relative to Section 306(a) or (b) of the Act, is provided on page 000009.

User Fee

Pursuant to the Prescription Drug User Fee Act of 1992, a check in the amount of (half the full fee for a new application with clinical data) was sent by certified mail to: Food and Drug Administration, P.O. Box 360909, Pittsburgh, PA 15251-6909 on November 20, 1996. A copy of the submitted User Fee Cover Sheet (Form FDA 3397) and check are enclosed on pages 000010 - 000011.

If there are any questions, or if assistance is needed during the review of this application, please contact me at (215) 751-4455 (telephone) or (215) 751-4096 (FAX).

Sincerely

Debra Hackett
Manager
U.S. Regulatory Affairs

Desk Copy: Ms. Maureen Dillon-Parker (Cover Letter/Item1: Volume 1.001)
Mr. David Bostwick (CRTs: Volumes 1.037 through 1.039)

SmithKline Beecham
Pharmaceuticals

December 13, 1996

Mr. David M. Moss
Director, Division of Information Systems Design
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, 8B-11
Rockville, MD 20857

General Correspondence: Equipment Loan for NDA Review

Dear Mr. Moss:

Reference is made to our New Drug application for Bactroban™ (mupirocin calcium) Cream (NDA 50-746) for the treatment of secondarily infected traumatic skin lesions.

SB has discussed with reviewers from the Anti Infective Division on several occasions the desirability of producing a CANDA for the mupirocin calcium submission. Based on these discussions and in light of the fact that NDA 50-746 comprises 817 volumes, it has become necessary for SB to loan the Center for Drug Evaluation and Research (CDER) equipment to facilitate the review of our computer assisted new drug application.

As requested, we are providing the following information regarding this loan:

1. Application Name and Number: Bactroban™ (mupirocin calcium) Cream (NDA 50-746)

2. Computer Hardware

Hardware:

3. Anticipated Date of Arrival: December 16, 1996

4. Delivered to

Ms Maureen Dillon-Parker (301-827-2125)
Division of Anti Infective Drug Products
Food and Drug Administration
9201 Corporate Blvd. (HFD-520)
Rockville, MD 20850

5. The equipment loan was necessary to support the review of the electronically submitted NDA.

All software provided is in full compliance with licensing agreements for that software.

We have taken precautions to ensure that the equipment and software are free of computer viruses and authorize CDER to use anti-virus software on the loaned equipment as appropriate.

We will arrange to take the equipment back as soon as the review is completed or the equipment is no longer needed for the review of this specific application.

We further understand that although the loan equipment and software is a temporary loan to help in facilitating the review, the data and possibly the media it is on, such as optical disk, diskette or hard disk is considered to be an official part of the NDA submission and, as such, may be retained by the Agency.

Please do not hesitate to contact me at (215) 751-4992 should you have any questions.

Sincerely yours,

John H. Wojcik.
Assistant Director, Canda Group
U.S. Regulatory Affairs

cc: Ms Maureen Dillon-Parker
Division of Anti Infective Drug Products

SmithKline Beecham
Pharmaceuticals

January 16, 1997

NDA 50-746
Bactroban® (mupirocin calcium cream) Cream, 2%

David Feigal, Jr., 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, MD 20850

General Correspondence

Dear Dr. Feigal:

Reference is made to our pending New Drug Application (NDA 50-746) for Bactroban® (mupirocin calcium cream) Cream, 2%, for the treatment of secondarily infected traumatic skin lesions.

Reference also is made to a telephone conversation on January 14, 1997 between Ms. Maureen Dillon-Parker (FDA) and the undersigned, in which the following information was requested.

Computer Assisted New Drug Application (CANDA)

We hereby wish to acknowledge that the electronic information in the CANDA version for *Bactroban* Cream is identical to the corresponding information in the " hardcopy" version of the NDA.

The CANDA contains the complete review copy of the NDA (Items 1 through 14) and consists of 817 volumes. The "hardcopy" portion of this NDA consist of 37 volumes only.

As previously communicated in our original submission of December 12, 1996, the following items are available as electronic files only as text searchable and/or electronic images:

- Published literature cited throughout the NDA except for the clinical publications.
- Item 10. Statistical Section: cross-reference to Item 8.
- Item 11. Case Report Tabulations.
- Item 12. Case Report Forms.

Preclinical - Statement of Compliance

To the best of our knowledge, all studies were conducted in compliance with the principles of the Good Laboratory Practice regulations for nonclinical laboratory studies intended to support the pending application for Bactroban® Cream.

If there are any questions, or if assistance is needed during the review of this application, please contact me at (215) 751-4455 (telephone) or (215) 751-4096 (FAX).

Sincerely

Debra Hackett

Debra Hackett
Manager
U.S. Regulatory Affairs

Desk Copy: Ms. Maureen Dillon-Parker
(Letter transmitted via facsimile 16 January 1997)

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

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: November 30, 1990
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASSIGNED**

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

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Pharmaceuticals	January 16, 1997
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101-7929	(215) 751-3868
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* NDA 50-746

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
mupirocin calcium cream	Bactroban® Cream, 2%

CODE NAME *(If any)*	CHEMICAL NAME
	(αE,2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
ical cream	topical	2%, 15 and 30 g tubes

PROPOSED INDICATIONS FOR USE

Treatment of secondarily infected traumatic skin lesions

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

IND	DMF	DMF
NDA 50-591	DMF	
NDA 50-703	DMF	

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

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

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

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ RESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☒ ORIGINAL APPLICATION ☐ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one)*

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

CONTENTS OF APPLICATION

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

X	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling *(12 copies)*
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case report forms (21 CFR 314.50 (f) (1))
	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))
X	15. OTHER *(Specify)* FDA request for information

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter, and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application on 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. 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.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Debra Hackett **Manager, U.S. Regulatory Affairs**	Debra Hackett	**January 16, 1997**

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
SmithKline Beecham Pharmaceuticals **One Franklin Plaza, P.O. Box 7929** **Philadelphia, PA 19101-7929**	**(215) 751-3868**

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Section 1001.)

SmithKline Beecham
Pharmaceuticals

ORIGINAL

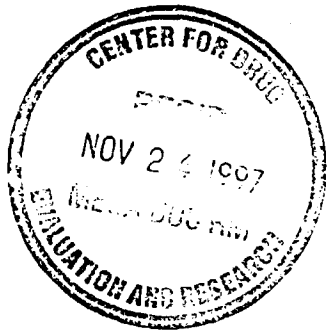
BC

November 21, 1997

NDA 50-746
Bactroban® (mupirocin calcium) Cream, 2%

Amendment - Change in Site for Identity Testing

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



Dear Dr. Chikami:

Reference is made to SmithKline Beecham's pending New Drug Application for Bactroban® (mupirocin calcium) Cream 2%, NDA 50-746. Specific reference is made to the conversation between Dr. David Katague (FDA Chemist) and the undersigned regarding the Agency's (Compliance) recommendation to withhold approval of this application due to GMP issues relevant to
is currently listed in the NDA as the site responsible for identity testing of the bulk cream prior to filling into 0.5g tubes.

At this time, we herewith wish to amend the application in order to replace as the facility used to perform the identity testing of the cream. The address is as follows:

will employ the exact method, i.e. the FTIR Identification Method as was originally planned by method and validation is included for ease of reference). A transfer of this method and validation to has been completed, and consequently is prepared to begin testing commercial bulk cream samples. Moreover, data derived from the first three commercial lots sent to will be provided to the Agency within the first Annual Report for this NDA.

is currently listed in NDA 50-746 as an alternate testing facility for both release and stability testing and has been deemed satisfactory by the Agency in terms of GMP.

We trust this satisfies the remaining CMC issue. If there are any questions regarding this amendment, please do not hesitate to contact the undersigned at 610-917-7723.

Sincerely,

Peter J. Kitz
Group Director
Worldwide Regulatory Support
Chemistry, Manufacturing, and Supply

Attachments

cc: Dr. David Katague - FDA-CDER/HFD-520