CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA19-832

Trade Name:Sulfamylon Powder for 5% Topical Solution

Generic Name:Mafenide Acetate, USP)

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: June 5, 1998

Indication: Orphan Drug designation and is indicated for use as an adjunctive top. antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 19-832

CONTENTS

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 19-832

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-832

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
Executive Director, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

JUN 5 1998

Dear Mr. Sisto:

Please refer to your new drug application dated February 18, 1988, and your resubmissions dated March 27, 1997 and April 17, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SULFAMYLON® (Mafenide Acetate, USP) Powder for 5% Topical Solution.

We acknowledge receipt of your submissions dated:

November 19, 1997
December 18, 1997
January 22, 1998
February 6, 1998
February 12, 1998
February 25, 1998
March 10, 1998
April 3, 1998
April 17, 1998
May 1, 1998
May 13, 1998

This new drug application has Orphan Drug designation and is indicated for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to recommend approval under the Accelerated Approval Regulations (21 CFR 314 Subpart H) with the draft labeling in the submission dated February 6, 1998, and revised as agreed in the letter of February 25, 1998. Accordingly, the application is approved effective on the date of this letter.

As acknowledged in the approvable letter of November 26, 1997, and in your submission of March 10, 1998, you have agreed to comply with the conditions of the Accelerated Approval Regulations (21 CFR 314 Subpart H).

Additionally, we acknowledge receipt of your May 28, 1998 facsimile in which you agree to modify the May 13, 1998, protocol in accordance with the facsimile from the Division of Anti-Infective Drug Products dated May 28, 1998 (attached).

The final printed labeling (FPL) must be identical to the draft labeling submitted on February 6, 1998, and revised as agreed in the letter of February 25, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 19-832. Approval of this submission by FDA is not required before the labeling is used.

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

We remind you of your commitments specified in your submissions dated January 22, 1998 and March 10, 1998. These commitments, along with any completion dates agreed upon, are listed below.

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

The Agency has granted 18 months of expiration dating for Sulfamylon finished product.

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

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

If you have any questions, please contact Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

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

Attachment: Facsimiles of May 28, 1998 (2 pages)

cc:
Original NDA 19-832
HFD-520/Div. files
HFD-520/CSO/M.Dillon-Parker
HFD-520/CLTL/Roberts
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)
HFD-520/MO/Bostwick MB 5/28/98
HFD-520/Chem/Timper 5/28/98
HFD-520/Pharm/Ellis 5/28/98
HFD-520/Micro/King 5/28/98
HFD-725/Stat/Li for YL 5/28/98
HFD-880/Biopharm/Ajayi
HFD-344/DSI/Thomas
HFD-160/Micro/Stinavage
HFD-160/Micro/Cooney

Concurrence:
HFD-520/CPMS/Bona 5/5/98
HFD-520/CTL/Roberts 5/28/98
HFD-520/MicroTL/Sheldon 5/28/98
HFD-520/PharmTL/Osterberg 5/28/98
HFD-725/StatTL/Lin 5/28/98
HFD-725/StatTL/Flyer
HFD-880/BiopharmTL/Pelsor 5/28/98
HFD-520/ChemTL/Katague 5/28/98

Drafted by: mdp/April 27, 1998/May 27, 1998/ap\N19832.ap
final: MDP 5/28/98

APPROVAL (AP) [with Phase 4 Commitments]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-832

NOV 26 1997

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
Executive Director, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Mr. Sisto:

Please refer to your new drug application dated February 18, 1988, and your resubmission dated March 27, 1997, received March 31, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SULFAMYLON® (Mafenide Acetate, USP) Powder For 5% Topical Solution.

We acknowledge receipt of your amendments dated:

June 23, 1997	July 25, 1997	October 9, 1997
June 24, 1997 (2)	August 29, 1997	October 28, 1997
June 27, 1997	October 8, 1997	November 4, 1997

This new drug application has Orphan Drug designation and is indicated for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information which was agreed to in your letter of November 4, 1997:

We acknowledge your commitment to comply with the conditions of Accelerated Approval (Subpart H; 21 CFR 314.500) as agreed in the telephone conversation of November 18, 1997, between representatives of this Division and Mylan. Additionally, we acknowledge your commitment to conduct the confirmatory clinical study as required under 21 CFR 314.510 and as discussed at the above teleconference.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling. If additional

information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

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

Attachment - Draft Labeling (5 pages)

cc:
Original NDA 19-832
HFD-520/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-520/M.Dillon-Parker
HFD-520/TLClin
HFD-104/Office Director
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-520/Clin/Bostwick 11-25-97
HFD-520/Pharm/Ellis 11/26/97
HFD-520/Micro/King 11/26/97
HFD-880/Biopharm/Ajayi 11/26/97
HFD-530/Stat/Li 11/26/97

Concurrence:
HFD-520/CPMS/Bona 11/25/97
HFD-520/ClinTL/Roberts 11/25/97
HFD-520/MicroTL/Sheldon 11/26/97
HFD-520/PharmTL/Osteberg 11/26/97
HFD-520/ChemTL/Katague 11/26/97
HFD-880/BiopharmTL/Pelsor 11/22/97
HFD-725/StatTL/Lin 11/26/97
HFD-530/StatTL/Flyer 11/1/97

Drafted by: mdp/November 19, 1997/n19832.ae
Initialed by: HFD-520/CHEM/TSUPER 11/26/97
Final:
HFD-160/Micro/Stinavage HFD-160/Micro/Cooney
APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

MEDICAL REVIEW(S)

NDA REVIEW OF NDA 19-832 RESUBMISSION
(CLINICAL REVIEW NO. 3)

Date of Resubmission: April 17, 1998. Other amendments dated January 22, February 6 and 25, March 10, April 3 and May 13, 1998.

Date CDER Received: April 20, 1998
Date Assigned to Reviewer: April 21, 1998
Date of Review Initiation: April 28, 1998
Date Review to Supervisor: May 18, 1998

Drug: Sulfamylon® Powder (Mafenide acetate for 5% topical solution)

Applicant: Mylan Pharmaceuticals, Inc.
Morgantown, WV 26504

Indication: "SULFAMYLON® For 5% Topical Solution is indicated for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds."

Directions for Use: The grafted area should be covered with one layer of fine mesh gauze. An eight-ply burn dressing should be cut to the size of the graft and wetted with SULFAMYLON® 5% SOLUTION using an irrigation syringe and/or irrigation tubing until leaking is noticeable. If irrigation tubing is used, the tubing should be placed over the burn dressing in contact with the wound and covered with a second piece of eight-ply dressing. The irrigation dressing should be secured with a bolster dressing and wrapped as appropriate. The gauze dressing should be kept wet. In clinical studies, this has been accomplished by irrigating with a syringe or injecting the solution into the irrigation tubing every 4 hours or as necessary. If irrigation tubing is not used, the gauze dressing may be moistened every 6-8 hours or as necessary to keep wet.

Wound dressings may be left undisturbed, except for the irrigations, for up to five days. Additional soaks may be initiated until the graft take is complete. Maceration of skin may result from wet dressings applied for intervals as short as 24 hours. Treatment is usually continued until autograft vascularization occurs and healing is progressing (typically occurring in about 5 days). Safety and effectiveness have not been established for longer than 5 days for an individual grafting procedure.

If allergic manifestations occur during treatment with SULFAMYLON® 5% SOLUTION, discontinuation of treatment should be considered. If acidosis occurs and becomes difficult to control, particularly in patients with pulmonary dysfunction, discontinuing the soaks with the mafenide acetate solution for 24 to 48 hours may aid in restoring acid-base balance. (See **PRECAUTIONS** section.) Dressing changes and monitoring the site for bacterial growth during this interruption should be adjusted accordingly.

Background: This NDA was made approvable on November 26, 1997. The application is subject to the provisions of Subpart H, CFR 314.500, which requires that a confirmatory clinical trial to confirm the clinical benefit of use of the product as recommended must be performed. Submission of FPL was also requested. The following submissions concerning these issues have been received since issuance of the approvable letter:

-January 22, 1998. Manufacturing control and microbiology submission.

-February 6, 1998. Submission of final printed labeling.

-February 25, 1998. Submission of revised DOSAGE AND ADMINISTRATION section of the labeling.

-March 10, 1998. Submission of revised Phase 4 protocol in response to FDA comments made in a February 26, 1998 teleconference between Mylan and HFD-520.

-April 3, 1998. Response to FDA comments on the phase 4 protocol made during an April 2, 1998 teleconference.

-April 17, 1998. Submission of revised Phase 4 protocol.

-May 13, 1998. Submission of revised Phase 4 protocol submitted in response to statistical comments faxed to Mylan on May 7, 1998.

Material Reviewed: The above submissions have been reviewed. This review will consist of the following sections:

1. Review of labeling

2. Review of revised Phase 4 protocol

3. Conclusions and recommendations

1. Review of labeling

The final printed package insert (FPL) submitted February 6, 1998 has been compared to the draft labeling sent to the applicant with the approvable letter. The FPL is identical to the draft. Subsequent to the submission of the FPL, the applicant requested permission to revise the first paragraph of the "Directions for Use of the Solution" subsection of the DOSAGE AND ADMINISTRATION section. The last sentence of this paragraph reads as follows in the FPL:

The applicant wishes to replace this sentence with the following:

This change was requested to reflect the technique used at Fort Sam Houston, TX over the period from 1972 to the present.

Reviewers Comment: **There is no objection to this revision. Revised FPL should be submitted when available.**

2. Review of revised Phase 4 protocol

Study Title: Comparison of Sulfamylon® 5% Solution and Standard Topical Therapy to Prevent Infectious Graft Loss in Patients with 20-60% Total Body Surface Area Thermal Injuries Requiring Meshed Autografts (Study No. SMS 401).

Investigators: To be determined. This will be a multi-center study conducted under a common protocol.

Study Objectives: The following is taken directly from the protocol submitted May 13, 1998:

> **To examine the incidence of Treatment Change and/or Infectious Graft Loss when Sulfamylon® (mafenide acetate) 5% Solution (SS5%) or other topical anti-infective agents are used as the initial topical moist dressing over meshed autografts on patients with thermal injuries to prevent bacterial infection.**

Method:

1. Study design: This is to be a multi-center, randomized, evaluator-blinded, parallel group comparison of the safety

and effectiveness of Sulfamylon Solution 5% and standard-of-care (SOC) in patients with 20-60% total body surface area (TBSA) burns requiring meshed autografts following surgical excision. A total of 300 patients will be entered into the study (150 in each group).

2. Inclusion criteria: The following is taken directly from the May 13, 1998 protocol:

1. Age: No restriction.
2. Sex: No restriction.
3. Number: 300 patients will be enrolled into this study.
4. Prospective study candidates must have a thermal wound with the following characteristics:
   a. Covers 20-60% Total Body Surface Area (TBSA).
   b. Is acute (initial hospitalization and within 7 days between excision and grafting).
   c. Requires surgical excision of the burn injury prior to grafting.
   d. Requires meshed autografts for all or part of the initial grafting procedure.
5. Patients (and/or legal guardians) are willing to sign an Informed Consent form.

3. Exclusion criteria: The following is taken directly from the May 13, 1998 protocol:

1. Known systemic allergy to sulfonamides or to sulfur-containing medication.
2. Time interval between burn injury and excision and grafting is greater than 7 days.
3. Grafting procedures which were conducted and/or evaluated on an outpatient basis.
4. Patients (and/or legal guardians) unwilling to participate.
5. Inability to use a meshed autograft as part of the initial grafting procedure.
6. Non-thermal burn injuries.
7. Thermal burn injuries greater than 60% TBSA.

4. Dosage and duration of therapy:

Grafts treated with Sulfamylon Solution will be re-moistened every 6-8 hours. The grafts treated with SOC will be re-moistened according to the protocol already existing at the

hospital. While each study center will not be required to have the same SOC, the patients within each center in the SOC group will receive the same SOC. In an effort to blind the study evaluations as much as possible, the dressings will be pre-soaked by hospital personnel not involved with patient care. The physician (or other patient care personnel) will thus apply the dressings without immediately being aware of which medication they contain.

All grafts will be evaluated at 48-72 hours after graft placement, at 5-7 days, at 10-12 days, and at 7 day intervals thereafter until time of discharge. The grafts will also be photographed . The usual procedure in grafts which have been successfully placed is to progress from the "wet" dressings described above to "dry" dressings, which are usually creams or ointments. Thus, the end of treatment for the "wet" dressings may vary by the size of burn, etc, although the change to "drys" can usually be accomplished 5-7 days after graft placement.

5. Study Evaluation Assessments: The following information will be collected at the time the graft is placed:

   a. Pre-surgical medication (especially antibiotics).

   b. Date and time of excision.

   c. Date and time of grafting.

   d. Date, time and frequency of application of randomized therapy. Changes in application frequency will be noted in the CRF.

   e. Extent of thermal injury (including a Burn Diagram) at the time of grafting.

   f. % TBSA grafted by type of graft used.

   g. Each graft procedure will be assigned a consecutive number beginning with "1", and each body site grafted during a particular procedure will be assigned a unique letter (i.e., "a").

   h. Photographic documentation of the graft procedure prior to dressing application.

The following information will be collected at each post-operative evaluation:

   a. Signs/symptoms of microbial colonization and/or localized infection

   b. % Graft take.

   c. Need for re-grafting of any graft procedure.

   d. Concomitant Medication.

e. Changes in randomized therapy, along with reason (s).

f. Clinical laboratory evidence of infection or adverse events.

g. Wound Assessment Score (attachment 1 to this review).

h. Photographic documentation of the initial graft procedure prior to dressing application.

6. Effectiveness Parameters: The following data will be presented for review for each treatment group (Sulfamylon and SOC):

1. **All Cause Graft Loss**: an autograft procedure was considered to have failed if there was autograft loss greater than 15% for any reason.

2. **Infectious Graft Loss**:

   a. An autograft procedure was considered to have failed if there was graft loss greater than 15% resulting from infection.

   b. If even one graft is classified as Infectious Graft Loss, then both the procedure and the patient would be classified as Infectious Graft Loss.

3. **Treatment Change**

   a. Defined as a change in topical antimicrobial treatment during the first five to seven days of application due to clinical judgement suggesting autograft jeopardy from infection or microbial colonization.

   b. The numbers of patients requiring Treatment Change will be tabulated and compared.

4. **Treatment Failure**:

   a. A combined endpoint reflecting either infectious graft loss or a change in topical antimicrobial treatment during the first five days of application as a result of infection or colonization.

   b. If even one graft is classified as a Treatment Failure, then both the procedure and the patient would be classified as a Treatment Failure.

5. **Wound Assessment Score**

6. **Regrafting**

   a. The number of patients and procedures requiring re-grafting will be tabulated by study medication received.

   b. The reason(s) for re-grafting will be noted in the case report form.

7. **% Graft Take** at each evaluation time.

7. Data Analysis (See Statistical Review for complete discussion):
The primary endpoint for this study is to be Treatment

Failure. All patients who complete at least 2 post-surgical evaluations will be considered evaluable.

There are two acceptable outcomes for this study:

a. Sulfamylon is proven to be superior to SOC in the primary endpoint.

b. Sulfamylon is proven to be equivalent to SOC in the primary endpoint, providing that information has been submitted on the SOC which establishes its usefulness in the desired indication.

Data will be stratified by burn size (20-40% and >40-60% TBSA). The study is to enroll 150 patients per group. This sample size (i.e., 150 patients per treatment group) will allow detection (alpha = 0.05) of (1) a 10% superiority between treatment groups when the success rate of the better therapy is ≥ 90% with 80% power and (2) equivalence when both treatments have success rates ≥ 90% (within 10%) with 80% power.

8. Safety: All adverse reactions and the treatment being administered at the time of the reaction will be recorded. Serious adverse events (death, prolongation of hospitalization, etc.) are to be reported to Mylan within 24 hours.

Reviewer's Comment:

The protocol is in general satisfactory. The following comments are relevant:

1. The exclusion criteria should include thermal injuries of less than 20% TBSA.

2. This will be an evaluator-blinded study. There will be many opportunities for the blind to be broken, especially if the SOC has a distinctive color or odor, but this system is probably the best which can be devised under the circumstances. Even so, precautions should be taken to insure that applications of the antimicrobial drug subsequent to the original application are blinded as much as possible. i.e., the patient should be blinded to the medication, and drug containers used at the bedside should be coded. Personnel making drug applications should not reveal

the drug used to the evaluators.

3. The information gathered at study entrance should include whether the patient suffered an inhalation injury.

Conclusions and Recommendations: The submitted labeling and Phase 4 protocol are satisfactory. Revised FPL (see Review of Labeling, above) should be submitted when available. This application may now be approved under subpart H of 21 CFR 314.500.

/S/

David Bostwick, Clinical Reviewer

/S/ 6/4/98

Rosemary Roberts, MD

CC: NDA 19-832
HFD-520/Division File
HFD-520/Bostwick/MO
HFD-Roberts/TL
HFD-520/Chem/Timper
HFD-520/Pharm/Ellis
HFD-520/Micro/King
HFD-725/Stat/Lin
HFD-520/PM/Dillon-Parker

Concurrence:
HFD-520/DivDir/Chikami
6/4/98

ATTACHMENT

CLINICAL REVIEW OF NDA 19-832 RESUBMISSION
(CLINICAL REVIEW NO. 2)

Date of Resubmission: March 27, 1997. Amendment dated July 25, 1997

Date CDER Received: April 1, 1997

Date Assigned to Reviewer: April 2, 1997

Date of Review Initiation: May 23, 1997

Date Review to Supervisor: September 23, 1997

Drug: Sulfamylon® Powder (mafenide acetate for 5% topical solution)

Applicant: Mylan Pharmaceuticals, Inc.
Morgantown, WV 26504

Related Applications:
1. IND

2. Approved NDA 16-763, Sulfamylon Cream (mafenide acetate 85 mg. Base per gm of cream)
   Applicant: Dow Hickam, Sugar Land, TX

3. IND

Proposed Indication: "SULFAMYLON POWDER® (Mafenide Acetate, USP) for 5% Topical Solution constituted to a 5% solution in Sterile Water for irrigation or 0.9% Sodium Chloride Irrigation, USP is indicated for use as a topical antibacterial agent to control bacterial colonization and to prevent infectious graft loss when used under moist dressings over meshed autografts on excised burn wounds."

Proposed Dosage and Administration: The following is taken directly from pp. 24-26 of the March 27, 1997 submission:

Not for Injection - For Topical Use Only

Directions for Preparation of the Solution - SULFAMYLON® (Mafenide Acetate) POWDER for 5% Topical Solution is to be constituted with Sterile Water for Irrigation, USP or 0.9% Sodium Chloride Irrigation, USP using aseptic techniques. Premeasured quantities of 50g of mafenide acetate powder are provided for constitution. Open the packet and empty the contents into a suitable container which contains 1000 mL of Sterile Water for Irrigation, USP or 0.9% Sodium Chloride Irrigation, USP. Mix until completely dissolved. Filter through a 0.2 micron

filter prior to use. This yields a 5% solution of mafenide acetate, USP. Use the solution within seven days after preparation. Store at controlled room temperature, 15° - 30°C (59° - 86°F). [19]

Directions for Use of the Solution - Cover the grafted area with one layer of fine mesh gauze. Cut an eight-ply burn dressing to the size of the graft and wet with the 5% solution of mafenide acetate in Sterile Water for Irrigation or 0.9% Sodium Chloride Irrigation using irrigation syringe and/or irrigation tubing. If a irrigation tubing is used, cover with a second piece of eight-ply dressing. Secure with a bolster dressing and wrap as appropriate. Keep eight-ply dressings wet by irrigating with a syringe or injecting the solution into the irrigation tubing. Wet the dressings until leaking is noticeable.

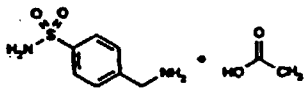
The dressing may be left undisturbed, except for the irrigations, for up to five days. Additional soaks may be initiated with corresponding changes in all dressings if indicated until graft take is complete.

If allergic manifestations occur during use of the mafenide acetate solution discontinuation of the soaks should be considered.

If acidosis occurs or becomes difficult to control, particularly in patients with pulmonary dysfunction, discontinuing the soaks with the mafenide acetate solution for 24 to 48 hours may aid in restoring acid-base balance. Dressing changes and monitoring the site for bacterial growth during this interruption should be adjusted accordingly, however.

Packaging: This product is to be provided in a 50 g packet.

Formulation: The product is mafenide acetate powder, USP (no excipients). The structural formula of mafenide acetate is as follows:



Regulatory History:

Reviewer's Note: The applicant has submitted a regulatory history which refers to NDA 6-613, which was also for a Sulfamylon 5% Solution product and was apparently marketed between 1948 and 1971, when it was withdrawn from the market. The files on that application are not available, and the following applies only to the product first submitted in 1988. This summary is adapted from the applicant's regulatory history and FDA files.

February 18, 1988 - Sterling Drug, Inc. filed a supplement to its approved NDA 16-763 for Sulfamylon Cream providing for a Sulfamylon 5% Solution, indicated as a topical antibacterial agent for adjunctive therapy in patients with second and third degree burns (same as cream indication). FDA classified this submission as a new NDA and assigned it the NDA number 19-832
April 25, 1988 - Clinical review (Huene) recommended non-approval because the submitted clinical studies were uncontrolled.
May 27, 1988 - Microbiology review (Creedon) recommended non-approval due to lack of *in vitro* susceptibility data.

July 11, 1988 - Chemistry review (Jarski) recommended non-approval due to packaging, stability and labeling deficiencies.
July 12, 1988 - Pharmacology review (Carlin) recommended approval.
November 8, 1988 - Not approvable letter issued.
February 27, June 19, September 25, 1989 - Meetings between Sterling and FDA to discuss protocols for controlled clinical studies.
July 18, 1990 - Sterling received Orphan Drug designation for the indication "topical antibacterial agent for use in prevention of graft loss of meshed autografts on excised burn wounds."
November 13, 1990 - Sterling responded to chemistry and microbiology deficiencies in the 1988 not approvable letter.
December 27, 1990 - Microbiology review #2 (Creedon) recommended approval.
May 24, 1991 - Sterling sold the NDA to Dow Hickam, Sugar Land, TX.
January 2, 1992 - Chemistry review #2 (Mokhtari-Rejali) recommended non-approval because sterilization of the product was not specified.
July 25, 1994 and January 30, 1995 - Meetings between Dow Hickam and FDA to discuss protocol for controlled clinical study.
April 6, 1995 - Statistical review (Turney) of paper by Livingston et.al. concerning the use of topical antimicrobials to prevent graft loss. Ms. Turney's review concluded that the study had procedural flaws which made its conclusions questionable.
June 6, 1995 - Meeting between Mylan/Dow Hickam and the Division of Anti-Infective Drug Products (DAIDP) to discuss protocol for controlled clinical study.
August 14, 1995 - Letter from DAIDP to Mylan requesting additional information to guide clinical protocol design.
August 29, 1995 - Dow Hickam received Orphan Drug designation for the indication "control of bacterial colonization under moist dressings over meshed autografts on excised burn wounds."
July 24, 1996 - Sulfamylon discussed by the FDA Anti-Infective Drug Products Advisory Committee. The Committee concluded that since topical antimicrobial solutions had evolved to a standard of care over the last 20 years, a placebo-controlled study would be unethical.
September 20, 1996 - Submission by Mylan of information concerning the toxicity of mafenide in wound healing and the association between bacteria and graft take.
August 15, 1996 and November 12, 1996 - Telecons between Mylan and FDA to discuss labeling and other issues.
January 28, 1997 - Meeting between Mylan and FDA to discuss data which are available from Shriners Burn Institute in Cincinnati.
March 12, 1997 - Mylan applied for a new Orphan Drug designation for the indication "for the control of bacterial colonization and to prevent infectious graft loss when used under moist dressings over meshed autografts on excised burn wounds".
March 25, 1997 - Rights to the NDA transferred from Dow Hickam to Mylan Pharmaceuticals.
March 27, 1997 - NDA resubmitted.
March 27, 1997 - Fax from HFD-520 to Mylan proposing time frame for performing genotoxicity study.

Background: Mafenide acetate is a sulfonamide drug which has an antibacterial spectrum roughly equivalent to that of silver sulfadiazine. Sulfamylon Cream (NDA 16-763) was approved in 1969 for use as adjunctive therapy in patients with second- and third- degree burns. The cream formulation has often been associated with pain on application, so it is not widely used. There have been reports that the drug and its primary metabolite inhibit carbonic anhydrase, causing acid-base disturbances and metabolic acidosis. Studies of absorption of the cream from the burn surface indicate that peak plasma concentrations are reached in 2-4 hours (Goodman & Gilman, 7th edition, 1985).

Because of the pain caused by the cream, burn physicians began to make a 5% solution using mafenide acetate powder in the mid-1970's (see IND list under Related Applications above). A number of individual investigator IND's have been submitted subsequently, and the 5% solution has become the standard of use in some burn units for maintaining skin grafts in the period between graft placement and graft take.

It should be noted that it is the understanding of the reviewers that the burn site is relatively "clean" (of microbial contamination) at the time of graft placement due to debridement/excision techniques. Thus, it is the task of topical antimicrobials to maintain a relatively low level of bacteria from the time of the surgical procedure with placement of the graft until the graft takes.

As can be seen from the Regulatory History above, the various drug applicants and DAIDP have had a difficult time with the study design of a clinical protocol to study 5% Sulfamylon Solution and have been unsuccessful. The principal difficulty has been the selection of a control group. The applicants have been reluctant to use a vehicle control on the grounds that failure to treat a burn patient with a total body surface area (TBSA) burn of larger than 10-20% would be unethical. The Anti-Infective Drugs Advisory Committee agreed with this position in the July, 1996 meeting which discussed Sulfamylon Solution. In addition, there are no approved topical antimicrobial solutions for the indication being sought.

Mylan Pharmaceuticals has subsequently submitted a retrospective study utilizing data from the Shriner's Hospital in Cincinnati, Ohio.

This study concerns comparison of patient records for those who received either a double-antibiotic solution (DAB) containing neomycin sulfate and polymyxin B or DAB plus Sulfamylon Solution 5%. DAIDP has agreed that this study might serve as basis for approval of Sulfamylon Solution (depending upon the results seen). There are also safety data available from retrospective studies of patients at the U.S. Army Institute of Surgery at Fort Sam Houston, Texas, as well as literature searches concerning the toxicity of mafenide in wound healing and the association between the presence of bacteria and graft take.

Material Reviewed: The applicant has submitted the following materials relevant to the safety and efficacy of the use of Sulfamylon Solution 5% (SS 5%) in human burn patients:

A. Pivotal Efficacy Study in Burn Wound Management of Children

Protocol No.	Design	No. Patients
91-02-20-04	Retrospective, non-randomized, parallel group, active control	281 DAB/SS5% 157 DAB alone

B. Supportive Safety Study in Burn Wound Patients

Protocol No.	Design	No. Patients
None	Retrospective, non-randomized, historical control	100

C. Literature Surveys (submission of September 20, 1996)

1. Review of Published Studies on Toxicity of Mafenide Acetate in Wound Healing

2. Review of Published Studies on Association between Graft Take and Bacteria

Reviewer's Comment: **This review will consist of the following sections:**

I. Review of Pivotal Clinical Efficacy Study

II. Review of Safety Studies

A. Retrospective safety study in burn patients at Fort Sam Houston, TX

B. Literature surveys
1. Toxicity in wound healing
2. Graft take vs. bacteria

C. Safety summary

III. Review of Labeling

IV. Conclusions and Recommendations

Other Reviews:

1. Pharmacology: In her review dated August 13, 1997, the reviewing pharmacologist, Dr. Amy Ellis, made the following recommendation:

> RECOMMENDATION: The pharmacologist has no objection to the approval of this NDA for Sulfamylon (mafenide acetate) Powder for 5% Topical Solution. The sponsor submitted data from an adequate genotoxicity (study) using mammalian cells as had been requested by the division so that the information could be included in the appropriate section of the label. The division agreed that the nonclinical data previously submitted for this drug product would be sufficient for supporting this NDA in consideration of Sulfamylon's long history of clinical use and the particular indications being sought for the product. The pharmacologist recommends that the sponsor be asked to modify the label for Sulfamylon as indicated above.

Her labeling recommendations were as follows:

2. Chemistry: In his review dated June 26, 1997, the reviewing chemist, Mr. Timper recommended that the application be made not approvable. He found deficiencies concerning stability and sterility assurance. Mr. Timper and Mylan are working to correct these deficiencies.

3. Biopharmaceutics: In her review dated October 28, 1997, the reviewer, Dr. Funmilayo Ajayi, made the following recommendation:

> **The submitted literature information is acceptable. The waiver for a need to demonstrate systemic bioavailability following topical application of the product is granted.**

4. Statistics: In her undated review, the reviewing statistician, Dr. Yulan Li, reached the following conclusion:

> **Based on the Cincinnati study, the applicant has demonstrated that the use of SS5% is associated with the decreasing of treatment failure in the subgroup of patients with 0-20% TBSA burns after separately adjusting for etiology and degree of burn. However, it is unknown whether the use of treatment failure reflects the benefit of adding SS5% to DAB due to non-random treatment assignment and investigator knowledge of treatment at the time treatment failure was assessed.**

Dr. Li's conclusions are also discussed in the Reviewer's Comment of section I. F.2.iii. of this review.

5. Microbiology: In his review dated June 10, 1997, the reviewing microbiologist, Dr. Robert Whiddon, reached the following conclusion:

> **The sponsor has used SS5% as an adjunct to therapy of autograft-treated burns. That therapy consists of debridement, use of DAB, and tissue grafts. The object of their submission is to demonstrate that graft "take" is enhanced with a regimen that includes the use of their drug. It is not possible to segregate individual organisms and evaluate their susceptibility against the drug when the submission did not have organism kill as its goal. The sponsor is making the claim that treatment with SS5% as an adjunct reduces autograft loss. This becomes a statistical comparison (differences in graft loss between groups treated or not treated with test drug). The primary thrust of the argument is that successful outcome is measured by graft success and not by measures involving organism kill. If the data submitted passes the scrutiny of the statistical reviewers, I recommend approval.**

A consultative review concerning the proposed sterilization procedure has been generated by Dr. Paul Stinavage, a microbiologist in HFD-160. In his review dated November 3, 1997, he reached the following conclusion:

The application is approvable pending resolution of Microbiology concerns. In order to expedite the review of this application, the review microbiologist has committed to a 3 day (business days) review of the submission of data submitted in response to the comments contained in this review.

I. Review of Pivotal Clinical Efficacy Study

A. Study Title: Use of 5% Mafenide Acetate (Sulfamylon) Solution in Burn Wound Management of Children (Protocol No. 91-02-20-04).

B. Investigator: Glenn Warden, M.D.
Shriners Burn Institute
Cincinnati, OH 45229

C. Study Dates: May 20, 1991 - October 13, 1995

D. Study Objectives: The following is taken directly from volume 5, p. 8-38 of the NDA resubmission.

To compare the efficacy and safety of DAB topical solution with or without the addition of SS5% topical solution on graft adhesion and microbial colonization/infection when applied every two hours as moist dressing over autografts on children with acute burn wounds who were treated at the Shriners Burns Institute.

E. Method:

1. Study design:This was a single-center, non-randomized, unblinded, parallel-group retrospective comparison of the safety and effectiveness of DAB Solution (neomycin sulfate 40mg/polymyxin B 200,000 units per liter) and DAB solution plus Sulfamylon Solution (5% mafenide acetate).

2. Inclusion and exclusion criteria: The following was taken from vol. 5, p. 8-38 of the resubmission:

The population under consideration included all acute burn patients admitted to the Shriners Burns Institute for grafting procedures between May 20, 1991 and October 13, 1995. The beginning of the period coincided with the opening of an Investigator-IND for the use of SS5% (IND This population includes patients who received SS5% (in combination with DAB or other topical antimicrobial solutions) under the IND, and patients who did not receive SS5%. The later group of patients served as the source of control patients. There was no protocol-specified assignment of patients to treatment with SS5%. This was a medical decision, made by the attending physician. In general, patients with large burn wounds, patients with wounds colonized with or infected by *Pseudomonas*, and patients thought to be at risk for the development of *Pseudomonas* colonization or wound infection were placed on a regimen containing SS5%.

The retrospective collection of data considered all acute burn patients treated during the target interval. From that perspective, exclusions were only made on the basis of: (a) not having an acute burn (e.g., grafting to treat Stevens-Johnson syndrome); (b) patients who were not treated with antimicrobials that could be compared to DAB/SS5% (in an incremental fashion); or (c) repeat admissions in the same individual.

3. Dosage and duration of therapy: The following is adapted from vol. 5, pp. 8-38 and 8-39 of the resubmission:

> Topical antimicrobial agents were used extensively to prevent bacterial colonization of the burn wounds, with two primary goals: a) prevention of invasive infection; and b) prevention of infectious graft loss. Usually, the entire burned area was treated with a topical antimicrobial preparation from the time a patient was admitted to the hospital until the wound was excised. At the time of excision or grafting, treatment was changed to a topical antimicrobial solution, consistent with the use of "wet" dressings. As a result, excised burn wounds, grafted areas, and frequently donor sites, were all treated with an antimicrobial solution for varying periods of time.
>
> After grafting, the wounds were dressed by placing fine mesh gauze directly over skin grafts followed by two layers of coarse mesh dressings. Rubber catheters were placed between the layers of coarse gauze so that the dressings could be irrigated every two hours with antibiotic solution. Dressings were secured in place with elastic wraps or stents. The dressings were kept "wet" in order to prevent graft loss from dessication prior to vascularization.
>
> The "wet" dressings were irrigated with an antimicrobial solution every two hours. Patients treated with DAB alone had their dressings irrigated with DAB every two hours. Patients treated with DAB/SS5% had their dressings irrigated with SS5% and DAB on an alternating schedule every two hours (i.e., SS5% - DAB - SS5% - DAB - etc.)
>
> In general, dressing changes and graft evaluations were conducted on post-operative Days 2 and 5. Vascularization of the graft was generally complete by Day 5. After vascularization, wet dressings were changed to a "dry" sterile dressing to prevent maceration of the graft and surrounding tissue. Topical antimicrobial coverage was continued in the form of an ointment or cream that was applied directly to the wound and covered with sterile gauze. Thus, therapy with DAB or DAB/SS5% usually lasted for 5 days. The "dry" sterile dressing was continued until graft margins were healed.
>
> Surgical practice included the routine use of perioperative antibiotics. Systemic antibiotics effective against common skin pathogens, often a first generation cephalosporin, were routinely used in the study population. In patients with evidence of infection or those considered to be at high risk, a combination of intravenous piperacillin, amikacin, and vancomycin (PAV) was sometimes employed. The use of perioperative antibiotics and the choice of individual agents was based on the medical judgment of the treating physician.

4. Effectiveness parameters: The following is adapted from pp. 8-43 to 8-47 of vol. 5 of the resubmission:

> Since this is a retrospective study, the applicant has set efficacy parameters based on the types of data collection.
>
> The following information was recorded for each graft procedure:
>
> - Date of procedure
> - Number of grafts
> - Sites covered in autograft or allograft
> - Area (TBSA %) covered in autograft or allograft
> - TBSA (%) treated with topical antimicrobial solution
> - Infecting organism(s)
> - Graft take (%) for autografts and allografts at Day 5 post-grafting & at additional times as necessary until healed

- Use of meshed autograft
- Reason for graft loss
- Reason for treatment change
- Pre- and post-grafting topical antimicrobial solutions and their start/stop dates

Based on this information, three endpoints were defined for evaluation of autograft take and loss:

a. All Cause Graft Loss

In this analysis, an autograft procedure was considered to have failed if there was autograft loss more than **15% for any reason.**

A topical antimicrobial treatment cannot be expected to have a positive influence on graft loss due to mechanical disruption, hematoma/seroma, or depth of injury. This endpoint would only be sensitive to a positive treatment-related effect if infection was the predominate cause of graft loss in the population under study. Thus, **All Cause Graft Loss** was included primarily to examine any potential negative impact from the addition of SS5% to DAB. As a result, this particular endpoint should be viewed more as an evaluation of the safety of SS5% in combination with DAB rather than a true measure of treatment effectiveness.

b. Infectious Graft Loss

In this analysis, an autograft procedure is considered to have failed if there is graft loss greater than **15% resulting from infection.**

Infectious Graft Loss is directly related to the goal of topical antimicrobial treatment and is therefore, more relevant to the assessment of drug effect than All Cause Graft Loss. The diagnosis of infectious graft loss was primarily a clinical diagnosis dependent on distinguishing signs and symptoms. Autografts that failed as a result of infectious causes were determined by the investigator.

c. Treatment Failure

Treatment Failure was defined as either infectious graft loss or a change in topical antimicrobial treatment during the first five days of application as a result of infection or colonization. For example, patients initially treated with DAB who required additional therapy with SS5% because of an emergent suppurative discharge would be classified as a DAB treatment failure by this analysis.

In general each autograft procedure was evaluated as a whole. However, there were a few complicated procedures which were evaluated in parts, with each part representing a separate grafting location. For analysis purposes these multi-part procedure evaluations were combined into a single evaluation using the following criteria:

- Graft take (%) for multi-part autograft procedures - the total autograft take for the procedure was calculated as the sum of graft take for each part times the area covered in autograft for each part. This sum was then divided by the sum of all areas covered in autograft for the procedure to obtain total autograft take for the whole autograft procedure.

- Reason for graft loss for multi-part autograft procedures - if the reason for graft loss was infection for any part of the procedure evaluation, then reason for graft loss was infection for the whole autograft procedure.

- Reason for treatment change for multi-part autograft procedures - if the reason for treatment change was a result of infection or colonization in the presence of signs of potential infection for any part of the procedure evaluation, then reason for treatment change was a result of infection or colonization in the presence of signs of potential infection for the whole autograft procedure.

The following variable was also proposed, but few observations concerning it are present in the Case Report Forms:

Microbial Prevalence

Cultures were usually obtained prior to grafting and with dressing changes (typically on Days 2 and 5 after the autograft procedure). As a result, most of the culture data occurs at those time points and data become increasingly sporadic beyond Day 5. Since time is considered to be an important factor in the risk of colonization or infection, prevalence was examined over time in both treatment groups.

The following definitions were used to determine microbial prevalence from the available culture data:

- Prevalence of a specific organism was defined as the number of individuals with at least one positive culture for that microbe during a fixed time period. Prevalence is expressed as a percentage of patients who had at least one wound culture obtained within the specified time period.

- Day 0 was defined as the date of the first procedure for each patient when it was known. If a patient was first treated elsewhere, the date of admission to Shriners Burn Institute was used as Day 0. Fixed time periods of interest were Pre-procedure and Days 0 - 2 (identified as Day 2 for data presentation), Days 3 - 5 (referred to herein as Day 5), and Days 6 - 10 (called Day 10 in this report).

Cultures were performed by surface swab from the graft sites. Semi-quantitative cultures were taken when appearance and/or odor indicated the possibility of infection.

The semi-quantitative terms can be related to microbial growth on the blood agar plate as follows:

- No growth
- Rare: $< 10^4$ = growth in thioglycolate broth only.
- Few: 10^4 = majority of colonies in the primary quadrant.
- Moderate: 10^5 = colonies extend into the second quadrant
- Many: $\geq 10^6$ = colonies extend into the third quadrant; too numerous to count.

<u>Reviewers Note:</u> No units are given for the colony counts (per g of tissue, mL, etc).

5. <u>Safety evaluation:</u> The following is taken directly from p. 8-43 of vol. 5 of the resubmission:

The CRF for the DAB/SS5% patients contained an adverse experience page that generally contained reference to only those events which could be differentiated from the injury and considered to be serious or drug-related. These serious adverse experiences were further verified against the IND safety reports submitted by the investigator. The presence or absence of pain, itching, rash, odor, and drainage was also assessed daily for each graft procedure maintained under topical solution therapy. Because of the previous association of dermal reactions and the use of sulfonamides and mafenide acetate, the investigator further evaluated all reports of rash. Details concerning these episodes were recorded on supplemental adverse experience pages.

Acid-base status was monitored using arterial blood gas measurements in patients who suffered inhalation injury and who were on ventilators. Plasma carbon dioxide concentrations were also recorded for some patients who were not on assisted ventilation. These data were not sufficient to allow for a systematic investigation of the incidence of mafenide acetate-induced metabolic acidosis. However, this data is (sic) presented herein for the sake of completeness.

F. Results:

1. Demographics: The investigator identified 671 patients as having received some form of topical medication as part of burn wound therapy during the period surveyed (May 20, 1991 - October 13, 1995). Eighty-four of these were excluded from analysis for the following reasons:

Not acute burn	69
Duplicate records	10
Not grafted	3
Not treated	2

Of the 587 patients who were treated for acute burns, 149 were excluded because they did not receive DAB or DAB plus SS5% as their initial topical therapy after autograft placement. Information on these 149 patients was submitted on July 25, 1997. This left 438 patients in the study. The following table, which is taken from volume 1, p. 2-66 of the NDA, describes the demographics for these patients.

The 149 patients who did not receive DAB or DAB plus SS5% will be described following the conclusions concerning the two main protocol groups. (Note: TBSA as used in this table means total body surface area.)

Table 1. Patient Demographics and Burn Injury Characteristics

	All Patients		
	DAB/SS5% (n = 281)	DAB (n = 157)	p-Value
Age (Years)			
Mean	7.1	6.4	
Standard Error	0.3	0.4	0.201
Range			
Sex [n (%)]			
Male	194 (69)	101 (64)	0.340
Female	87 (31)	56 (36)	
Race [n (%)]			
Caucasian	221 (79)	127 (81)	
Black	50 (18)	25 (16)	0.893
Other	10 (4)	5 (3)	
Allergy to Sulfa Drugs			
Yes [n (%)]	4 (1)	1 (0.6)	
No [n (%)]	227 (99)	156 (99)	0.659
Etiology of Burn [n (%)]			
Flame	196 (70)	74 (47)	
Scald	73 (26)	57 (36)	
Chemical	1 (0.4)	2 (1.3)	<0.001
Electrical	2 (0.7)	1 (0.6)	
Contact	9 (3)	23 (15)	
TBSA with 3° Burns (%)			
Mean	23.0	5.7	
Standard Error	1.3	0.7	<0.001
Range			
Total % TBSA Burned			
Mean	28.8	9.7	
Standard Error	1.3	0.8	<0.001
Range			
Length of Hospital Stay (Days)			
Mean	32.6	14.9	
Standard Error	1.9	1.0	<0.001
Range			

p-Values for continuous variables are from Student's t-test; those from discrete distributions are from Fisher's Exact Test.

Reviewer's Comment: Because of the retrospective nature of this study, there are many elements which imbalance the test groups. Among them are:

1. **The group which received both DAB and SS5% had much larger (TBSA) and serious (3°) burns than did the group which received DAB alone.**

2. **Almost half the autografts in the group which received both treatments were meshed, while of only about 8% of the grafts in the DAB alone group were meshed.**

3. **Many different types of concomitant medications and treatments were used in the treatment of these patients, including systemic antibiotics, other topical antimicrobials, etc.**

The concomitant therapies were used on an as needed basis, with the more serious burns requiring more intensive treatment modalities. The data collected on the CRF's include only the names of antibiotics and drugs that were used. Dose, route of administration, etc. are not available. Thus, the effect of concomitant medications in this study is largely unknown.

It can be seen that straightforward comparison of the treatment groups would not provide an adequate evaluation of the usefulness of SS5%. There are other questions about the data which do not appear to be answerable, and so will not be pursued, although they do bear mentioning. For instance, it is not clear what criteria were used in adding SS5% to the treatment regimen in patients with small burns (20% or less). This was again a purely clinical judgement which the reviewers do not question, but it makes the analysis of data difficult in that the criteria for use of SS5% are not clear.

2. Graft Take/Treatment Failure Results:

i. 40% TBSA or more

It is noted that those patients with 40% or more TBSA are almost exlusively DAB/SS5% recipients. Only one patient in this group needed DAB alone. Further, the various treatment modalities used on these very serious burns are varied, and the concomitant medications used were numerous. For instance, the following list of concomitant medications other than DAB and SS5% is furnished for patient S-014, who had a 53% TBSA burn, 20.5% of which was third degree (dosage regimens are listed when given in the CRF):

Pre-operative meds
Silver sulfadiazine
Gentamicin ophthalmic ointment
Amikacin
Piperacillin
Vancomycin

Post-operative meds
Nystatin (q 6)
Polymyxin B (qd)
Tobramycin ophthalmic ointment (q 12)
Amikacin
Piperacillin
Vancomycin
Potassium acetate
Sodium carbonate
Augmentin
Sodium Sulamyd ophthalmic ointment
Kefzol
Silver sulfadiazine
Sodium bicarbonate
Bacitracin
Hibiclens

This is not an unusual list for patients with similar burns. Since in most cases the duration and dosage of the concomitant medications are not known, it is impossible to assess the contribution of SS5% to the total treatment effect. For the sake of completeness, the data on the greater than 40% TBSA patients are presented in outline form. Although the data have been summarized in terms of 20% increments in TBSA burned, it must be noted that these patients do not present a uniform picture, and conclusions should not be drawn from the data. (Please see also the Reviewer's Note below).

In the data listings below, the following conventions have been used:

1. TBSA (%) is the mean total body surface area burn for the group under consideration.

2. TBSA 3° (%) is the mean total body surface area with third-degree burns for the group under consideration.

3. n Surv. (%) is the number of patients and percentage of the total in the group who survived therapy to the point where they could be discharged from the hospital.

4. Phys. Assess presents the assessment of the physician (Dr. Warden) in terms of the number of patients and % of the TBSA Subgroup of the effectiveness of Sulfamylon in the therapy using the following grading scale:

    1. No colonization/No graft loss
    2. Colonization/No infectious graft loss
    3. Colonization/Minimal infectious graft loss
    4. Colonization/Significant graft loss

5. Graft take presents the initial range of graft take in % for each patient in the TBSA Subgroup. It must be noted that many graft procedures which initially failed were later successfully repeated. .

6. Graft Loss presents the reasons for graft loss. One patient may have had a number of different reasons for graft loss. If infection was one of the reasons, the reviewers have chosen that one to present. Graft loss codes are as follows:

1 = unknown
2 = hematoma or mechanical
3 = infection
4 = poor base

TBSA Subgroup	TBSA (%)	TBSA 3° (%)	n Surv. (%)
40-60% (n=42)	50.4	42.1	37 (88%)
61-79% (n=23)	70.5	56.1	17 (74%)
80% or greater (n=7)	84.5	78.2	4 (57%)

	TBSA Subgroup		
Phys. Assess.	40-60% (n=42)	61-79% (n=23)	80% or more (n=7)
1	5 (12%)	1 (4%)	1 (14%)
2	9 (21%)	5 (22%)	1 (14%)
3	20 (48%)	9 (39%)	0
4	8 (19%)	8 (35%)	5 (71%)

	TBSA Subgroup		
Graft Take	40-60% (n=42)	61-79% (n=23)	80% or more (n=7)
90-100%	17 (40%)	4 (17%)	0
80-100%	3 (7%)	0	1 (14%)
70-100%	7 (17%)	8 (35%)	0
60-100%	5 (12%)	1 (4%)	2 (29%)
50-100%	2 (5%)	1 (4%)	2 (29%)
<50-100%	8 (19%)	9 (39%)	2 (29%)

	TBSA Subgroup		
Graft Loss	40-60% (n=42)	61-79% (n=23)	80% or more (n=7)
1	4 (9%)	2 (9%)	0
2	11 (26%)	3 (13%)	1 (14%)
3	22 (52%)	15 (65%)	6 (86%)
4	5 (12%)	3 (13%)	0

Pathogenic Organism Results

For those patients who had infectious graft loss, the causative pathogens have been noted (except in one case, where the pathogen is unknown). Typically, there were multiple organisms cultured from the same graft or from multiple grafts on the same patient.

There may have been 3 or 4 organisms identified for a single patient, and these have been listed separately. The following list represents the number of times an organism was identified as being associated with graft loss, either alone or in combination with other organisms. On a per-patient basis, the list represents patients who have already been treated at least once with SS5% (except in one case-see Reviewer's Comment #2, below).

Organism	n (% of 72 patients)
Pseudomonas aeruginosa	26 (36%)
Candida albicans	20 (28%)
Staphylococcus aureus	14 (19%)
Escherichia coli	8 (11%)
"Fungus"	8 (11%)
Enterococcus	5 (7%)
Klebsiella species	4 (6%)
Coagulase negative staphylococci	3 (4%)
Proteus species	2 (3%)
Staphylococcus aureus (methicillin resistant)	2 (3%)
"Yeast"	2 (3%)
Enterobacter species	2 (3%)
Acinetobacter species	2 (3%)
Serratia marcescens	1 (1%)
Bacillus species	1 (1%)
Xanthomonas maltophilia	1 (1%)
Aspergillus species	1 (1%)

Safety Results: It is difficult to assess the association of adverse events to drug therapy in these severely ill patients. When a patient died, the reason for death was reported as an adverse event, though the final event was caused by a number of processes which may or may not have been drug related. It may be said that it is impossible to directly implicate SS5% or DAB in any of the systemic reactions reported, though the topical reactions may be drug associated. Some patients had more than one reaction.

Adverse event	n
Respiratory insufficiency	6
Sepsis	4
Multiple organ system failure	3
Amputation	3
Coagulation disorder	2
Itching	2
Convulsions	1
Vascular occlusion	1
Seizure, hearing loss	1 had both
Neuropathy: decreased hearing and vision	1 had both
Cerebrovascular accident	1
TOTAL -	25; 25/72 = 35%

Reviewer's Comment: **It is remarkable that so many of these severely burned children survived to leave the hospital. As noted above, it is difficult to assess the effect of individual medications on these patients because they were treated in so many different fashions. It is not unexpected that survival rates fall as TBSA burned increases. The following items should be noted:**

1. **There were a few inconsistencies in the physician's assessment of whether graft loss was due to infection vs. the reasons for graft loss as given in the CRF's. That is, the physician occasionally evaluated the graft as "no colonization/no infectious graft loss" while the CRF designated an organism as contributing to loss of a graft. However, these evaluations were in general consistent.**

2. **There was only one patient in this group who did not receive Sulfamylon . This patient was also the only patient in this group who had no third degree burns (he had a 49% TBSA second degree burn). His therapy with DAB was successful.**

3. **There were two patients , who were originally treated only with DAB and were later switched to SS5% because of *Pseudomonas aeruginosa* infections. These patients both survived and were subsequently released from the hospital.**

4. **Although SS5% is useful against *Pseudomonas aeruginosa*, 36% of the patients in this group incurred some graft loss which was associated with *Pseudomonas aeruginosa* even after SS5% was used.**

ii. 20-40% TBSA

Emphasis has been given to this group of patients because there are a few patients (15) who received DAB alone, so it may be possible to make some comparisons between DAB and DAB/SS5% use. Further, while concomitant medications were used in all these patients, such use post-operatively was somewhat less than in the larger burns. Finally, the reviewers have learned in discussions with burn surgeons that burns of smaller size (1-20% TBSA) would be expected to accept a graft with much less dependence on topical anti-microbials. Thus, it may be that the 20-40% TBSA group is the one in which the contribution of topical antimicrobials to graft take can be demonstrated without the confounding effect of numerous concomitant medications in all patients.

a. Demographics and Burn Characteristics

	All Patients	
	DAB/SS5% (n=88)	DAB (n = 15)
Mean age in years	6.38	7.25
Sex [n (%)]		
Male	58 (66)	9 (60)
Female	30 (34)	6 (40)
Race [n (%)]		
Caucasian	67 (76)	12 (80)
Black	18 (20)	2 (13)
Hispanic	3 (4)	1 (7)
Etiology of Burn [n (%)]		
Flame	64 (73)	13 (87)
Scald	23 (26)	2 (13)
Contact	1 (1)	0
Mean % TBSA with 3° Burns	19.5	12.6
Mean % TBSA Burned	28.9	24.3
Patients Artificially Ventilated [n (%)]	17 (19)	3 (20)
Mean No. procedures / Mean No. grafts	1.42 / 6.07	1.0 / 4.27

Reviewer's Comment: **Although the groups are greatly imbalanced in size, they are reasonably similar in demographic characteristics. The DAB/SS5% group had about a 50% greater mean third degree TBSA burn than the DAB alone group. The DAB/SS5% group also had more procedures on the average than the DAB alone group, although most patients in both groups had only one procedure. The DAB/SS5% had about 50% more individual grafts per patient than did the DAB alone group.**

There are no obvious reasons for assignment of a patient to the DAB or DAB/SS5% groups. However, there were seven patients in this group who had second-degree burns only. Four of these patients (4/88=4.5%) were begun on DAB/SS5% and three on DAB alone (3/15=20%). (See also the Treatment Switch results below).

b. Graft Take/Treatment Failure Results: Almost all patients in this group had good initial graft take. Typically, at least minimal graft loss took place as medications were adjusted, with the final graft take returning to very high levels. Thus, a patient might begin with 98% graft take, slip to 90% at a week from surgery, and return to 98% in 2 to 3 weeks from surgery.

In addition, therapy was usually switched from DAB or DAB/SS5% after 5 days of treatment as a matter of course. The reviewers have evaluated each CRF to determine whether therapy at the end of 5 days could be termed successful in terms of graft take and reasons for topical therapy change. The applicant has provided nine possible reasons for graft loss. One of these was "infection." If the graft was found to be infected at the time of topical therapy switch from DAB or DAB/SS5%, it was evaluated as a failure by the reviewers, even if the graft take percentage remained relatively high. (It is noted that all graft loss of 15% or more was associated with infection with one exception. That exception was graft loss secondary to a hematoma.)

Also, the applicant has provided a list of eleven reasons for change of topical treatment. If at the time of topical therapy switch from DAB or DAB/SS5% the reason for change was one of the three listed below, the graft procedure was evaluated as a failure by the reviewers:

1. Infectious graft loss (per microbiological evidence with positive cultures)
2. Infectious graft loss (per clinical evidence without positive cultures)
3. Inadequate control of colonization with potential for graft loss, evidenced by odor and/or drainage.

If the investigator notes associated graft loss or switch in topical therapy with the presence of odor and/or drainage, the procedure was evaluated as a failure even if the applicant's code did not indicate one of the above reasons for loss on switch.

In the tabulations below, individual procedures are presented separately. That is, if a patient had two separate procedures, that patient will be represented twice in the tables. The time of assessment in this tabulation was during the 5 days after the graft procedure.

Reviewer's Note:
The reviewers have evaluated a procedure as a failure if: the investigator noted infection connected with the loss; if the investigator's reason for switching topical therapies was infectious graft loss with or without culture evidence, or inadequate control of colonization; or the investigator notes switch in therapy associated with odor and/or drainage. This means that the outcomes as stated in the application were changed in many instances.

Number and % of Procedures with Antimicrobial Failure and Success

	DAB/SS5% (n=125)	DAB alone (n=15)
Success	80 (64%)	10 (67%)
Failure	45 (36%)	5 (33%)

c. Graft Loss Causes: The reasons for graft loss for the individual procedures are listed below. Some procedures were assigned more than one reason for graft loss. If "infection" was one of the reasons given, it is listed here and the other reasons are not listed.

	Graft Loss Reasons	
Graft Loss Code	DAB/SS5% (n=125)	DAB alone (n=15)
Unknown or none	24 (19%)	6 (40%)
Hematoma or mechanical	49 (39%)	4 (27%)
Infection	45 (36%)	5 (33%)
Poor base	7 (6%)	0

d. Physician Assessment: The reviewers changed many of the results that the physician felt were successful to failures (See Reviewer's Note above). Therefore, the physician assessments are more favorable to the drug therapies than the graft take results would suggest.

This is a global assessment per patient (not per procedure).

	Physician Assessment	
Physician Assessment Code	DAB/SS5% (n=88)	DAB alone (n=15)
No colonization/No graft loss	22 (25%)	5 (33%)
Colonization/No infectious loss	44 (50%)	5 (33%)
Colonization/Minimal infectious loss	17 (19%)	3 (20%)
Colonization/Significant graft loss	4 (5%)	1 (7%)
Not stated	1 (1%)	1 (7%)

e. Treatment Switches: As noted above, all DAB alone or DAB/SS5% patients were routinely switched to other therapies after 5 days of treatment. However, there were 4/15 (27%) patients in the DAB alone group who were switched to DAB/SS5% earlier than 5 days because the DAB alone was not effective. One of these patients failed on DAB/SS5% also, and eventually expired. One patient was switched from DAB/SS5% to DAB alone because he was progressing and the investigator felt SS5% was no longer needed.

f. Survival Rates: Nearly all patients in this TBSA group survived. In addition to the patient described in e. above, two patients initially treated with DAB/SS5% expired before they could be discharged from the hospital.

g. Safety Results: Again, if a patient expired, the events associated with the death were reported as adverse events. It is impossible to directly associate SS5% or DAB with any of the more serious reactions, though the topical reactions in this group may possibly be associated with SS5% and/or DAB. Some patients had more than one reaction. In the table, "S" refers to DAB/SS5%, and "D" refers to DAB alone.

Adverse event	n and Treatment Group
Itching, rash	1 S, 1 D
Burning	1 S
Heart arrest	1 S
Dermatitis	1 S
Respiratory insufficiency	1 S
Sepsis, multiple organ system failure	1 S, 1 D
Pneumonia, dehydration	1 each in 1 S pt.
TOTAL =	7 S, 2 D

The rates are 7/88 = 8% for the DAB/SS5% group, and 2/15 = 13% for the DAB alone group.

l. Concomitant Medications: All patients received some form of medication before grafting; a typical regimen was silver sulfadiazine cream, bacitracin cream, and/or Kefzol. Those patients who had infectious organisms detected during the post-operative period had a variety of topical and systemic antimicrobials added to their therapy in order to prevent/treat the infection. Since the pre-operative regimens were fairly standard, and since the grafting procedure presumably left a relatively clean wound surface after completion, it is not felt that the pre-operative medications lead to misinterpretation of the effect of the post-operative medications. In the case of the post-operative infections, those procedures were evaluated as failures when the patient had concomitant antimicrobial medications and, thus, do not confuse the analysis.

However, many patients who were evaluated as successes by the reviewers also had post-operative medications. Because record-keeping for those medications was sketchy (no dosage or duration is available in the CRF's), it is difficult to judge how much effect they had on the success of the procedure.

Thirty-four of eighty (43%) of the DAB/SS5% procedures which were evaluated as successes by the reviewers did not have any post-operative concomitant antimicrobials listed on their charts. Eight of ten (80%) of the DAB alone successful procedures did not have any post-operative concomitant antimicrobials listed. For the most part, the post-operative medications used on the DAB/SS5% patients were combinations of topical and systemic medications. Since the procedures were apparently progressing well, it is not clear why these drugs were administered.

i. Pathogenic Organisms: For the patients who had infectious graft loss or whose topical therapy switch was associated with infection, the causative organisms have been noted. Typically, there were multiple organisms cultured from the same graft or from the multiple grafts on the same patient. All such organisms have been listed. The following tabulation represents the number of times an organism was identified as being alone or in conjunction with other organisms in the same patient.

	n (% of total procedures)	
Organism	DAB/SS5% (n=125)	DAB alone (n=15)
Pseudomonas aeruginosa	19 (15%)	3 (20%)
Candida albicans	11 (9%)	2 (13%)
Staphylococcus aureus	8 (6%)	1 (7%)
Enterobacter species	5 (4%)	0
Serratia marcescens	5 (4%)	1 (7%)
Bacillus species	4 (3%)	1 (7%)
Gram-negative rods	3 (2%)	1 (7%)
Group D enterococcus	3 (2%)	1 (7%)
Klebsiella species	3 (2%)	0
Coagulase negative staphylococcus	2 (2%)	1 (7%)
Escherichia coli	2 (2%)	0
Proteus mirabilis	2 (2%)	0
Acinetobacter species	1 (1%)	0
Acinetobacter baumanii	1 (1%)	0
Aeromonas hydrophilia	1 (1%)	0
Enterobacter cloacae	1 (1%)	0
Enterobacter agglomerata	1 (1%)	0
Morganella morganii	1 (1%)	0
Streptococcus species	1 (1%)	0

Reviewer's Comment: The data summarized above are suggestive that the treatment regimen which adds SS5% as opposed to DAB alone performed better with respect to organisms cultured from the graft site. However, superiority is not proven because there were so few patients in the DAB alone group, and because the effect of concomitant medications in the DAB/SS5% group is not known. Even so, the following points should be noted:

1. **The treatment groups had equivalent success rates in the procedures performed, even though the DAB/SS5% group had about a 50% greater mean third degree TBSA burn than the DAB alone group. The DAB/ SS5% group also had more mean procedures and grafts than did the DAB alone group. This is favorable for DAB/SS5% because larger third degree burns with more grafts present a more difficult infection control problem than smaller, less severe burns.**

2. **Four of 15 patients in the DAB alone group were switched the DAB/SS5% because of lack of effectiveness. Three of these patients proceeded to successful outcomes with the use of DAB/SS5%.**

iii. Less than 20% TBSA

This group of patients has by far the largest number of DAB alone patients in it. Unfortunately, it is the understanding of the reviewers that when grafts are applied for these smaller burns, antimicrobial therapy is often not needed, i.e., graft take in these 0-20% TBSA burns is sometimes not dependent on the use of antimicrobial therapy. The applicant asserts in its summary that superiority can be shown for the variables graft loss and treatment failure in this group.

a. Demographics and Burn Characteristics

	All Patients DAB/SS5% n = 121	DAB n = 142
Mean age in years	6.74	5.68
Sex [n (%)]		
Male	85 (71)	90 (63)
Female	36 (29)	52 (37)
Race [n (%)]		
Caucasian	95 (79)	116 (82)
Black	21 (17)	22 (15)
Hispanic	3 (2)	1 (1)
Other	2 (2)	3 (2)
Etiology of Burn [n(%)]		
Flame	72 (59)	64 (45)
Scald	38 (31)	52 (37)
Contact	8 (7)	23 (16)
Chemical	1 (1)	2 (1)
Electrical	2 (2)	1 (1)
Mean % TBSA with 3° Burns	7.0	3.4
Mean % TBSA Burned	10.5	7.0
Patients with 2% Burns Only [n (%)]	5 (4.1)	24 (16.9)
Patients Artificially Ventilated [n (%)]	12 (9.9)	4 (2.8)
Mean No. Procedures/Mean No. Grafts	1.11/3.21	1.04/2.10*

* This information missing for 2 patients.

Reviewer's Comment: The groups are reasonably similar in demographic characteristics. In terms of type and severity of burn, the DAB/SS5% patients had twice as much body surface area involved with third degree burns than the DAB alone patients, although with averages this small it is unclear that this is a clinically meaningful difference. It is certain that there were significantly more patients in the DAB alone group who had second degree burns only. These burns are presumably easier to treat. In general, it may be stated that the DAB/SS5% patients on entry had more severe burns than did the DAB alone group. See Evaluable Patients below.

a. Evaluable Patients: Two patients in the DAB/SS5% group were excluded because of the severity of their injuries. Patient had a 70% TBSA burn originally which was grafted successfully initially. However, about 15% TBSA of the original grafts failed and he was returned for regrafting. It is felt that this patient did not have injuries similar to the others in this group. Patient died on the fifth day of therapy due to severe inhalation injury. At that time, no graft loss had been seen. One other patient died due to cardiac arrest secondary to inhalation injury, after hospital discharge. It is felt that the data are sufficiently complete for this DAB/SS5% patient to permit inclusion in the study.

Two DAB alone patients have been excluded from analysis because their records are incomplete (no graft take data, etc.).

There were concomitant medications used in all patients in this group. As in the 20-40% group, a typical pregrafting treatment regimen included silver sulfadiazine, bacitracin, and/or Kefzol. It is felt that since these medications were reasonably consistently administered, and since the grafting process left a relatively clean wound surface, their use does not confuse the interpretation of the topical antimicrobial therapy used post-operatively.

There were a number of patients who also had post-operative topical and systemic medications. There is no reason to exclude the data for those patients whose procedure was judged to be a failure by the reviewers. However, because the dosages and durations of therapy are unknown, the following patients whose procedures were otherwise judged to be successful by the reviewers have been declared not evaluable for efficacy since the contribution of DAB/SS5% or DAB cannot be determined:

DAB / SS5%
(4 procedures)

DAB alone

(1 of 2 procedures)

(1 of 2 procedures)

(2 procedures)

A summary of the reasons for exclusion:

Reason	DAB/SS5% (n)	DAB (n)
Concomitant medications	29	13
Data missing	0	2
Expired in hospital	1	0
Inconsistent w/other patients	1	0
	31	15

It is useful to restate the burn characteristics for the evaluable patients.

	DAB/SS5% n = 90	DAB alone n = 127
Etiology of Burn [n (%)]		
Flame	54 (60)	60 (47)
Scald	28 (31)	44 (35)
Contact	6 (7)	20 (16)
Chemical	1 (1)	2 (1)
Electrical	1 (1)	1 (1)
Mean % TBSA with 3° Burns	6.5	3.3
Mean % TBSA Burned	10.6	7.0
Patients with 2° Burns Only [n (%)]	4 (4.4)	22 (17.3)
Patients Artificially Ventilated [n (%)]	3 (3.2)	2 (1.5)
Mean No. Procedures/Mean No. Grafts	1.11/2.83	1.01/2.06

Reviewer's Comment: The burn characteristics of the two groups remain relatively the same with the exception that most of the artificially ventilated patients have been disqualified for concomitant medications.

b. Graft Take / Treatment Failure Results: Most of the comments made concerning the 20-40% TBSA burn group are applicable to the 0-20% group. Once again, individual procedures are presented. This tabulation differs from the 20-40% TBSA tabulation in that only evaluable patients are included. (No patients were excluded from the 20-40% TBSA tabulation.)

Number and % of Procedures with Antimicrobial Failure and Success

	DAB/SS5% (n* = 100)	DAB alone (n* = 129)
Success	81 (81%)	96 (74%)
Failure	19 (19%)	33 (26%)

* number of procedures in evaluable patients

c. Graft Loss Causes: The comments made for the 20-40% TBSA group also apply here.

	Graft Loss Reasons	
Graft Loss Code	DAB/SS5% (n* = 100)	DAB alone (n* = 129)
Unknown or none	44 (44%)	62 (48%)
Hematoma	35 (35%)	32 (25%)
Infection	19 (19%)	33 (26%)
Poor Base	2 (2%)	2 (2%)

* number of procedures in evaluable patients

d. Physician Assessment: The comments made for the 20-40% TBSA group also apply here. This is a global assessment per patient (not per procedure).

	Physician Assessment	
	DAB/SS5%	DAB alone
Physician Assessment Code	(n = 90)	(n = 127)
No colon/no loss	46 (51%)	64 (50%)
Colon/no inf. loss	37 (41%)	38 (30%)
Colon/min. inf. loss	7 (8%)	21 (17%)
Colon/sig. inf. loss	0	3 (2%)
Not stated	0	1 (1%)

e. Treatment switches: In the presentation below, the "Switch" category indicates the number of patients whose therapy was switched from DAB/SS5% or DAB alone in less than 4 days from graft placement because of infection or suspicion of infection (the surgeon often made these switches without confirmatory cultures). "Switch to SS5%" indicates the number of patients who were switched from DAB alone to DAB/SS5% because of infection or suspicion of infection. The tabulation concerns number of procedures rather than individual patients.

	DAB/SS5% (n = 100)	DAB alone (n = 129)
Switch	1 (1%)	20 (16%)
Switch to SS5%	0	16 (12%)

One patient failed on both topical medications and was switched to a third before colonization was controlled.

f. Safety Results: The comments made for the 20-40% TBSA group also apply here. Once again, "S" refers to DAB/SS5% and "D" refers to DAB alone.

Adverse event	n and Treatment Group
Hypertension	1 S
Amputation	1 S
Rash	1 S
Respiratory distress	1 S
Cardiac arrest secondary to inhalation injury	1 S
Death secondary to inhalation injury	1 S
Hives	1 D
TOTAL =	6 S, 1 D

6/121 = 5% DAB/SS5%; 1/142 = 1% DAB alone

g. Pathogenic organisms: Some patients in this group were not tested by culture for pathogenic organisms. For those patients who had infectious graft loss or whose topical therapy switch was associated with infection, the causative organisms have been noted when available. When multiple organisms were identified, all are listed. There were 5 DAB/SS5% procedures and 36 DAB alone procedures for which no cultures were taken. The "n" has been adjusted to reflect this.

	n (% of total procedures)	
Organism	SS5% / DAB (n = 95)	DAB alone (n = 93)
Pseudomonas aeruginosa	6 (6%)	13 (14%)
Enterobacter cloacae	3 (3%)	5 (5%)
Coagulase negative staphylococcus	3 (3%)	4 (4%)
Staphylococcus aureus	2 (2%)	4 (4%)
Escherichia coli	2 (2%)	4 (4%)
Proteus mirabilis	2 (2%)	2 (2%)
Acinetobacter species	1 (1%)	1 (1%)
Candida albicans	1 (1%)	1 (1%)
Acinetobacter baumanii	0	1 (1%)
Acinetobacter lwoffi	1 (1%)	0
Bacillus species	1 (1%)	0
Gram-negative rods	1 (1%)	0
Group D enterococcus	0	1 (1%)
Klebsiella species	1 (1%)	0
Serratia marcescens	0	1 (1%)
Yeast	1 (1%)	0

Reviewer's Comment: This portion of the study (less than 20% TBSA burns) provides information suggesting the superiority of the combination of Sulfamylon Solution and DAB over DAB alone in the control of bacterial colonization and the prevention of graft loss when used as part of a regimen of moist dressings over autografts placed on burn wounds. (Since DAB alone has not been approved for the desired indication, it must be considered as a placebo in the review of this study.) This superiority is supported by the following:

1. **Patients who received alternating applications of DAB and DAB/SS 5% had more serious burns than those patients who received DAB alone. This is substantiated by the numbers of evaluable patients with second degree burns only (4.4% of the DAB/SS 5% patients vs. 17.3% of the DAB alone patients, p - value = 0.004). Even so, the DAB/SS 5% group did as well as the DAB alone group in terms of anti-microbial effectiveness in the maintenance of autografts (81% vs. 74% successes, p-value = 0.35).**

2. **When the number of patients is compared who were able to complete 4 days of therapy using the prescribed topical treatment regimen, regardless of whether the procedure was judged a success, 99% of the DAB/SS 5% patients vs. 84% of the DAB alone patients were successful (p-value = 0.002). More importantly, 12% (16 total) of the DAB alone patients were switched to DAB/SS 5% and 15 of these patients successfully completed the initial phase of antimicrobial treatment using the combinations.**

3. **In terms of safety, there was one reaction in each group (rash in DAB/SS 5%, hives in DAB alone) which was probably or possibly associated with topical drug therapy.**

One area which is questionable concerning these conclusions is disqualification of patients due to concomitant medications. Many more (29 vs. 13) patients who would otherwise have been successes in the DAB/SS 5% group vs. the DAB alone group had concomitant medications after graft placement. One obvious determinant appears to be the need to ventilate the patients. Nine of the 29 disqualifications in the DAB/SS 5% group were artificially ventilated. These patients may have been more compromised by their damaged lungs than the non-ventilated patients and, therefore, may not have responded as well to antimicrobial treatment. As a group, the disqualified DAB/SS5% patients also had relatively large TBSA burns (12.5% mean) and TBSA 3° burns (7.9% mean). It is likely that the greater severity of burns in general of the DAB/SS 5% patient group accounts for the more frequent use of concomitants.

Dr. Yulan Li in her statistical review has evaluated the endpoints as proposed by the sponsor using all patients in the study (the subset of evaluable patients was not available at the time her review was finished). Therefore, she has done what amounts to an Intent-to-Treat analysis on the data base. She finds no significant superiority for DAB/SS 5% over DAB alone in any of the sponsor's endpoints when the patients with 0-40% TBSA burns are considered. As noted above, it is felt by the clinical reviewers that the only group with a sufficient number of DAB only patients to support a meaningful comparison is the 0-20% TBSA group.

For the 0-20% TBSA group, Dr. Li finds no statistically significant superiority for DAB/ SS 5% except in the category Treatment Failure (infectious graft loss or change in topical antimicrobial treatment during the first 5 days of therapy) at Day 5 and at last graft assessment. Thus, it appears that the clinical reviewer (using evaluable patients and a rather strict means of evaluating the success of therapy) and the statistician (using all available patients and the sponsor's endpoints and evaluations) have reached the same general conclusion.

It should also be noted that it appears that topical antimicrobial therapy is used in the majority of even these small burns. While graft loss may be rare in these burns, these data suggest that colonization and subsequent infection are common enough to make such therapy advisable. In a telephone conversation between Dr. Warden and Mr. Bostwick (September 17, 1997), Dr. Warden stated that the results of this study have caused him to begin <u>all</u> his graft patients on the combined SS5%/DAB regimen.

3. <u>Results from Patients Not Receiving DAB or SS5%:</u>

1. <u>Demographics</u>: The following table, adapted from pp. 37 and 38 of vol. 11.1 of the NDA, describes the demographics of the 149 patients who did not receive either DAB or DAB/SS5%.

Table 1. Patient Demographics and Burn Injury Characteristics (n=149)

Age (Years)	Mean Standard Error Range	6.1 0.4
Sex [n (%)]	Male Female	90 (60) 59 (40)
Race [n (%)]	Caucasian Black Other	118 (79) 30 (20) 1 (1)
Allergy to Sulfa Drugs	Yes [n (%)] No [n (%)]	2 (1) 147 (99)
Etiology of Burn [n (%)]	Flame Scald Chemical Electrical Contact	75 (50) 37 (25) 1 (1) 5 (3) 31 (21)
TBSA with 3° burns (%)	Mean Standard Error Range	16 2
% TBSA Burned	Mean Standard Error Range	19 2 0.2-84.0
Length of Hospital Stay (Days)	Mean Standard Error Range	27.5 5.5
Distribution of Burn Wound Size (TBSA Burned) [n (%)]	0-20% 21-40% > 40%	96 (64) 25 (17) 28 (19)

Reviewer's Comment: These burns are similar to the burns treated with DAB or DAB/SS5%. It is not apparent from these data why these patients were not included in the DAB/SS5% study.

2. Concomitant Medications: The following table, taken from p. 41, vol. 11.1 of the NDA, lists the preoperative and concomitant systemic antibiotics in these patients.

Table 2. Use of Systemic Periopative Antibiotics [n (%)]

Systemic Antibiotics	N=149
Administered PreSurgically	
Keflex/Kefzol	88 (59)
Amikacin	34 (23)
Piperacillin	34 (23)
Vancomycin	34 (23)
Nystatin	13 (9)
Polymixin B	8 (5)
Amoxicillin	6 (4)
Other	25 (17)
Systemic Concomitant Antibiotics	
Cefazolin	72 (48)
Amikacin	51 (34)
Vancomycin	50 (34)
Piperacillin	49 (33)
Nystatin	37 (25)
Neomycin	7 (5)
Amoxicillin	5 (3)
Nafcillin	5 (3)
Polymyxin B	5 (3)
Other	36 (24)

The following table, adapted from p. 95, vol. 11.1 of the NDA, lists the topical antimicrobial medications used in these patients (n=149).

Table 3. Use of Concomitant Topical Antiseptics

Drug	n (%)
Bacitracin, Top	43 (28.9)
Chlorhexidine	29 (19.5)
Silver Sulfadiazine	22 (14.8)
Polymyxin B, Top	10 (6.7)
Nystatin, Top	7 (4.7)
Other	11 (7.4)

3. Results: It is the opinion of the reviewers that the most important information available in this patient group concerns those who did not receive any topical antimicrobial medications. Some of the patients received more than one of the topical and/or systemic medications listed above, but 34 patients have been identified who received no postoperative topical or systemic antimicrobials immediately. The demographic information for these patients will

not be described fully. However, the following information is indicative of the types of burns seen in this group.

Table 4 - Burn description

Etiology of Burn	n (%)
Flame	12 (35)
Scald	5 (15)
Contact	14 (41)
Electrical	3 (9)

Mean TBSA with 3° Burns (%) - 0.69

Mean % TBSA Burned - 1.50

Reviewer's Comment: **It is apparent that at Dr. Warden's facility, only burns of very small size are not treated with concomitant antimicrobials. This supports the observation of the Anti-Infective Drugs Advisory Committee that it would not be practical to perform a placebo-controlled study in support of the usefulness of SS5% in burns.**

It should also be noted that 20 of these 34 patients eventually received topical bacitracin prior to discharge, usually for prophylactic purposes.

II. Review of Safety Studies

A. Retrospective safety study in burn patients at Fort Sam Houston, TX

1. Study Title: Retrospective Review of Current and Historical Use of Sulfamylon ® (mafenide acetate USP) 5% Topical Solution In The Treatment of Burned Soldiers: 1968-1996.

2. Investigator: Basil Pruitt, M.D.
US Army Institute of Surgical Research (ISR)
Fort Sam Houston, TX 78234

3. Study Dates: This study consists of a survey of 100 burn patients admitted to the ISR from January, 1995 to April, 1996. Data from use of SS5% at the facility since 1972 are also discussed.

4. Method: This study is exclusively a report concerning the adverse events seen in the patients described under Study Dates. In general, those patients were treated with SS5% to protect cutaneous auto-grafts or freshly excised wounds which were not grafted. Dressings were soaked with SS5% every 6-8 hours and left in place 3-5 days. Data on other medications used are not available.

5. Results

A. Demographics: The following tables, which are taken from p. 8-1922 of vol. 10 of the NDA, describe the demographics of the 100 burn patients seen from Jan. 1995-April 1996.

Table 1. Description of Patients Comprising the Most Recent 100 Burn Cases

Gender	Parameter	N	Mean	SD	Minimum	Maximum
Females	Age (years)	14	42	26		
	Height (cm)	14	152.3	27.4		
	Weight (kg)	14	59.84	26.89		
Males	Age (years)	86	34	22		
	Height (cm)	81	164.3	29.5		
	Weight (kg)	86	70.9	30.0		

Table 2. Summary of Burn Characteristics of the Most Recent 100 Burn Cases at Fort Sam Houston

Parameter	N	Mean	SD	Minimum	Maximum
TBSA Burned	100	16.8	13.0		
% Full Thickness Burns	100	6.5	10.5		
% Total 2nd Degree Burns	100	10.4	9.3		
Total % Grafted	93	13.0	11.7		
# Days in SS5% Wraps	97	14.1	9.7		

b. Adverse events: There were 4 patients (4%) in the cohort who developed pruritic rashes while being treated with SS5%. These responded to antihistamines and drug discontinuation.

There were 4 deaths in patients in the cohort. These deaths were not related to SS5% therapy. Three of these patients had extensive inhalation injuries, and the fourth suffered cardiopulmonary arrest.

The applicant has also surveyed the annual reports to IND which has been in effect since the early 1970's. The years monitored were 1972-1992. In that time period, there were 2,797 patients treated with SS5% at ISR. There were 201 reports (7%) of rash in the patients as well as 6 reports of pulmonary/cerebral complications (apparently hyperventilation and/or mental confusion). These phenomena may have been related to impaired renal function with accompanying metabolic acidosis.

The applicant has also provided two relatively recent references which concern studies in which SS5% was used in the management of burn patients. These are:

1. Kucan JO, Smoot EC. Five percent mafenide acetate solution in the treatment of thermal injuries. *J Burn Care Rehabil* 1993; 14:158-63.

2. Lee JJ, Marvin JJ, Heimbach DM, Grube BJ. Use of 5% sulfamylon (mafenide) solution after excision and grafting of burns. *J Burn Care Rehabil* 1988; 9:602-605.

In the first (Kucan) paper, the authors treated 669 patients over a 7 year period with SS5%. The mean TBSA in these patients was 17.1%, with a mean third-degree burn area of 9.5%. In 276 of the patients, SS5% was used as the primary initial topical antibacterial agent. Pain during application occurred in 22% of the patients, while rash and pruritus occurred in 2.4% and 2.1% of patients, respectively.

In the other 393 patients, SS5% was used after the initial topical antimicrobial was discontinued. SS5% was discontinued in 4.5% of these patients due to pruritus or rash.

In the second (Lee) study, adverse events were surveyed in 67 patients who had had been treated with SS5% over a 13 month period. Pain of some degree was seen in over 60% of the patients, with 18% displaying a rash. Four of the patients (6%) displayed symptoms of metabolic acidosis.

B. Literature Surveys

1. Toxicity in wound healing

At the request of DAIDP reviewers, the applicant has submitted a literature survey concerning the potential of mafenide acetate to delay wound healing. Most of the references submitted are from *in vitro* or animal studies. The following summaries concern the papers which the reviewers consider most relevant.

a. McCauley RL, Linares HA, Pelligrini V, Herndon DN, Robson MC, Heggers JP. *In vitro* toxicity of topical antimicrobial agents to human fibroblasts *J Surg Res* 46:267-274, 1989.

Human fibroblasts were exposed *in vitro* to silver sulfadiazine (concentrations from 0.01 to 0.05%) and mafenide acetate (concentrations from 0.1 to 1.0%). In both cases, there was a significant reduction in cell proliferation.

b. Cooper ML, Laxer JA, Hansbrough JF. The cytotoxic effects of commonly used topical antimicrobial agents on human fibroblasts and keratinocytes. *J Trauma* 31(6):775-782, 1991.

Human fibroblasts and keratinocytes were exposed to 10 commonly used topical antibacterial agents. The highest dose tested for mafenide was 0.85%. Only Neosporin GU irrigant had no significant effect on these cells. Mafenide appears to be more toxic to keratinocytes than fibroblasts. Silver sulfadiazine could not be tested in the system used in this study.

c. Smoot III EC, Kucan JO, Roth A, Mody N, Debs N. *In vitro* toxicity testing for antibacterials against human keratinocytes. *Plast Recon Surg* 87(5):917-924, 1991.

Human keratinocytes were exposed to 7 commonly used topical antibacterial agents. When used at a concentration of 5%, mafenide acetate permitted 99% of the cells to survive, as opposed to 47% survival for a 0.03% solution of silver sulfadiazine. By using three separate test methods, the authors arrived at an antibacterial toxicity rating based on 100 for saline to 0 for most toxic. Using this scale, mafenide was rated at 73, silver sulfadiazine at 47, and povidone-iodine at 29.

d. McCauley RL, Li Y, Poole B, Evans MJ, Robson MC, Heggers JP, Herndon DN. Differential inhibition of human basal keratinocyte growth to silver sulfadiazine and mafenide acetate. *J Surg Res* 52:276-285, 1992.

Human keratinocytes were exposed to silver sulfadiazine (concentrations from 0.01 to 0.05%) and mafenide acetate (concentrations from 0.1 to 1.0%). More severe toxicity was seen in the mafenide acetate assays. The authors state that this implies that inhibition of wound epithelialization is greater with mafenide acetate than with silver sulfadiazine.

e. Zapata-Sirvent RL, Hansbrough JF. Cytotoxicity to human leukocytes by topical antimicrobial agents used for burn care. *JBCR* 14:132-140, 1993.

Human lymphocytes and neutrophils were treated with silver sulfadiazine (dose 0.004%) and mafenide acetate (dose 0.85%). Both drugs inhibited lymphocyte and neutrophil function.

f. Reilley DA. Sensitivity of cultured human melanocytes to topical drug delivery. ABA proceedings 1995.

Human melanocytes were exposed to various topical antimicrobials, including Sulfamylon at 5% and 4 unspecified diluted strengths (but not silver sulfadiazine). Hibiclens was toxic to the melanocytes at all concentrations. Sulfamylon was toxic at 5% and inhibitory when diluted.

g. Scapicchio AP, Constable JD, Opitz B. Comparative effects of silver nitrate and Sulfamylon acetate on epidermal regeneration. *Plast Recon Surg* 41(4):319-322, 1968.

(The following is based on the applicant's abstract of this paper.)
The purpose of this study was to compare the effects of silver nitrate solution (0.5 per cent) and Sulfamylon Cream, 11.2% on epidermal regeneration in an experimental wound in the normal healing of which infection is unimportant. Full thickness noncontracting wounds were made in rabbits. Wounds were treated with 0.9% sodium chloride solution, 0.5% silver nitrate solution, Sulfamylon Cream or Sulfamylon base placebo. Wounds treated with saline, silver nitrate and Sulfamylon placebo began to reepithelialize at day 5 whereas Sulfamylon Cream treated wounds began at day 15. Sulfamylon placebo treated wounds healed on average at day 17. Sulfamylon Cream treated wounds healed on average at day 28. Although both silver nitrate solution and Sulfamylon Cream have been used in controlling burn wound sepsis, there does appear to be a difference in their effects on epidermal regeneration in the absence of significant infection.

h. Billote JB, Koumans RJK, Guthy EA, Constable JD, Burke JF. Effect of topical Sulfamylon on wound healing. *Surg Forum* 20:71-73, 1969.

(The following is based on the applicant's abstract of this paper.)
In this study, full thickness wounds were made in guinea pigs. Wounds were treated with Sulfamylon Cream 11.2% twice daily, treated with Sulfamylon placebo twice daily or left untreated. Wound contraction rate, histology and radioautography and hydroxyproline content for each treatment were observed. Wound healing proceeded normally for both the Sulfamylon placebo and the untreated controls and was complete by day 27. Wounds treated with Sulfamylon Cream were noted to have necrosis of three major cellular participants before day 12. Excessive granulation tissue was noted later in the healing process. By day 37, signs were still evident of local necrosis of the regenerating epithelium. Topical Sulfamylon Cream delays wound healing because of its destructive effect on the three major cellular participants.

i. Argamaso RV, Garcia A. Freiman M, Lewin ML, Bharati S. Effect of Sulfamylon acetate on wound healing. *Plast Recon Surg* 46:282-287, 1970.

These authors made 4 observations:
- When half of the donor area for a human skin graft was treated with Sulfamylon Cream and the other half with gauze, no delay in healing on the Sulfamylon side was noted.
- Superficial wounds made on rats and either treated with Sulfamylon Cream or left untreated displayed no differences in healing at 15 days.
- Full thickness wounds made on rats and treated with Sulfamylon Cream, silver nitrate or left untreated found the silver nitrate-treated wounds more fully healed at day 10, but no difference between the groups by day 17.
- Full thickness wounds made on rabbits and treated with Sulfamylon Cream or saline resulted in all saline wounds healed by day 19, but only half the Sulfamylon treated wounds. The authors concluded that Sulfamylon Cream caused a retardation in epithelial migration.

j. Burleson R. Effect of skin dressings and topical antibiotics on healing of partial thickness skin wounds in rats. *Surg Gyn Ob* 136:958-960, 1973.

Partial thickness wounds were made on the backs of rats and were left untreated or covered with porcine skin, silver sulfadiazine or Sulfamylon Cream. One group was intentionally infected with *Staphylococcus aureus* and not treated. The wounds covered with porcine skin healed in 8 days, the untreated wounds healed in 12 days, and the wounds covered with silver sulfadiazine and Sulfamylon Cream healed in 17 and 18 days, respectively. The wounds seeded with *S. aureus* healed in 19 days.

k. Kjolseth D, Frank JM, Barker JH, Anderson GL, Rosenthal AI, Acland RD, Schuschke D, Campbell FR, Tobin GR, Weiner LJ. Comparison of the effects of commonly used wound agents on epithelialization and neovascularization. *J Am Coll Surg* 179:305-312, 1994.

Full-thickness wounds were made on male hairless mouse ears. These were treated with 500 units/g bacitracin, 0.25% sodium hypochlorite, 0.5% silver nitrate, 1% silver sulfadiazine, 8.5% mafenide acetate or 10% povidone-iodine. Control wounds and wounds treated with silver sulfadiazine and mafenide acetate epithelialized in 7 days. Wounds treated with povidone-iodine epithelialized in 12 days, with the other groups falling between 7 and 12 days.

l. Bellinger CG, Conway H. Effects of silver nitrate and Sulfamylon on epithelial regeneration. *Plast Recon Surg* 45:582-585, 1970.

Twelve donor sites in 9 patients were utilized in this experiment. The central third of each site was covered with Xeroform gauze. The remaining thirds were treated with either 0.5% silver nitrate or Sulfamylon Cream. Both active preparations were changed twice daily. The Xeroform covered portion of the wound healed on an average of 7 days, while the silver nitrate covered portions healed on an average of 10 days and the Sulfamylon covered portion healed on an average of 13 days.

2. Graft take vs. bacteria

The applicant has submitted a literature survey which examines the relationship between bacterial levels and graft take. The following summaries concern the papers which the reviewers consider most relevant.

a. McManus, AT, Parnell LKS, Tizard IR. Experimental association of meshed autograft loss and bacterial surface contamination. *Wound Rep Reg* 3:97, 1995.

(The complete publication was not available for review. The following is from the abstract.) Skin was harvested from rats, expanded 3:1 and stapled back onto the donor sites. The rats were randomized into 3 treatment groups; saline only, *Pseudomonas aeruginosa* with saline, and *Pseudomonas aeruginosa* with 5% mafenide acetate. The initial level of *P. aeruginosa* was 10^5 CFU/graft. Graft take was evaluated after 96 hours. Graft take was significantly inferior in the *P. aeruginosa*/saline group (1 out of 12 took) as compared to the other 2 groups.

b. Jackson DM, Lowbury EJL, Topley E. Pseudomonas pyocyanea in burns. *Lancet* 2:137-147, 1951.

This and the following paper are classic studies which were among the first to explore the relationship of bacteria and graft take. This study had a number of progressive phases. They may be summarized as follows:

i. Patients were randomized to treatment with polymyxin 0.1% in cream or spray, or placebo. Eleven of 160 (7%) of the polymyxin-treated burns were colonized with *Pseudomonas pyocyanea,* while 50/207 (24%) of the placebo burns were colonized.

ii. Patients were again randomized to polymyxin or placebo, and graft take evaluated. Fourteen of 55 (25%) of grafts took in the control group, as compared to 24/39 (62%) in the polymyxin-treated group.

iii. The same treatment groups were investigated in a different group of patients in terms of healing time. Sixteen of 28 (57%) of the polymyxin treated full thickness burns were healed within 4 weeks, while 8 of 43 (19%) control patients were healed in this time frame.

c. Jackson DM, Lowbury EJL, Topley E. Chemotherapy of *Streptococcus pyogenes* infection of burns. *Lancet* 2:705-711, 1951.

This paper also included a number of phases. The most relevant to this review is the portion which compared a topical penicillin cream to placebo cream in the prophylaxis of burns against *Streptococcus pyogenes*. 2% of 58 burn sites receiving penicillin were colonized with *S. pyogenes*, as opposed to 38% of 42 burn sites which received the placebo cream.

d. Robson MC, Heggers JP. Bacterial quantification of open wounds. *Military Med* 134:19-24, 1969.

In this paper, 50 consecutive patients with burns, ulcers or other full thickness skin loss were treated randomly with various topical agents (0.5% silver nitrate, 10% Sulfamylon Cream, 0.1% Garamycin Cream) prior to grafting. It was found that for those wounds which had bacterial levels of 10^5 organisms per gram of tissue or less, graft take averaged 96%. If the count was greater than 10^5 organisms, average graft take was less than 20%. Similar results were seen in a separate study of pressure sores.

e. Robson MC, Krizek TJ. Predicting skin graft survival. *J Trauma* 13:213-217, 1973.

(The following is adapted from the abstract presented by the applicant.) Thirty patients with granulating wounds requiring split thickness skin grafts were biopsied for bacterial quantification prior to receiving homografts every 48 to 72 hours until "take" was obtained. One hundred eleven biopsies and homograft applications were performed. In all cases at the time of homograft "take", the bacterial count in the graft bed was 10^5 or fewer bacteria per gram of tissue. Conversely, in 77 of the 81 homograft tests in which a "take" did not occur, the bacterial count was greater than 10^5 organisms per gram to tissue.

f. Livingston DH, Cryer HG, Miller FB, et al. A randomized prospective study of topical antimicrobial agents on skin grafts after thermal injury. *Plast Reconstr Surg* 86:1059-1064, 1990.

This paper was reviewed by Ms. Elizabeth Turney, an FDA statistician, in 1995. The following is adapted from her review.

This is a single-center, randomized, parallel group study which compares Ringer's Lactate, neomycin 1gm/liter plus bacitracin 50,000 units/liter and silver nitrate 0.5% as topical dressing solutions for the prevention of graft loss. After the grafting procedure, gauze dressings were applied and soaked with one of the test solutions every 2-6 hours.

After 45 of the planned 90 patients were enrolled, the study was discontinued because graft loss was high in the Ringer's Lactate group (Ringer's Lactate does not contain an antimicrobial) and the rapid emergence of resistant organisms in the neomycin plus bacitracin group. Ms. Turney concluded that because additional silver nitrate patients were added during the course of the study, it could not be accepted as statistically valid.

g. Herndon, DN, Kraft ER. Temporary reduction of burn wound quantitative bacterial counts to $<10^2$ with subsequent 95% overall autograft survival. *Surg. Forum* 33:61-63, 1982.

(The following is adapted from the abstract presented by the applicant.) Preparation of contaminated burn wounds with $\geq 10^5$ organisms/gram of tissue with mafenide acetate cream was tested for reduction in quantity of bacteria in the wounds and subsequent skin autograft survival. Twenty-six patients with full thickness skin loss contaminated with $\geq 10^5$ colony counts of bacteria were treated intermittently with mafenide acetate and silver sulfadiazine. Mafenide acetate treatment was stopped after three to four quantitative biopsies (6 to 10 days) when $<10^2$ organisms were obtained. All patients received split thickness autografts when their conditions were medically stable and when wound biopsies were $< 10^2$ organisms/gram. Twenty-five of the twenty-six patients treated intermittently with mafenide acetate and silver sulfadiazine whose wounds were $<10^2$ organisms/gram of tissue had 100% skin autograft survival.

c. Safety summary

Sulfamylon Solution 5% is reasonably safe when used topically over grafted skin on burn wounds. Because burns cause many accompanying systemic complications, it is difficult to connect many of the serious adverse events seen during the conduct of Dr. Warden's study to Sulfamylon use. It is highly unlikely that the reported episodes of sepsis, respiratory insufficiency, cardiac arrest, etc. were due to Sulfamylon. Even the topical reactions seen (itching, rash, etc.) could have been connected to the use of DAB in conjunction with Sulfamylon.

However, since the patients at Fort Sam Houston were (apparently) treated topically only with Sulfamylon, the topical reactions seen can fairly be ascribed to it. There was a 4% rate of pruritic rashes in the recent 100 patient cohort as well as a 7% rate in the 2,797 patients included as part of the annual reports from the facility from 1972-1992.

There were also 6 reports of possible metabolic accidosis in the 2,797 patient group. Dr. Warden screened his patients for this phenomenon, but did not report any. This may have been because the Sulfamylon applications were rotated with DAB, which allows acid-base balance to be more easily maintained.

The question of whether mafenide acetate retards wound healing is not easily answered. The only study in humans (Bellinger, 1970) used Sulfamylon Cream, which is more concentrated and has an irritating vehicle. The animal and *in vitro* studies reviewed do not present a consistent picture, and many of these studies also used Sulfamylon Cream. There does seem to be sufficient evidence available to justify inclusion of a statement in the labeling concerning the possibility of delayed wound healing caused by contact with mafenide acetate.

Although the connection of bacterial levels to graft take is more closely identified with efficacy than safety, it will be discussed here. There is adequate evidence available in the literature to establish that wounds (including burn wounds) may be expected to progress satisfactorily if the microbial load present is reduced to less than 10^5 organisms per gram of tissue. Unfortunately, the microbial assays performed in Dr. Warden's study were inconsistently applied, and quantitative results were not made available (except in a very few cases) for the patients reviewed. Nevertheless, it may be said that if a topical antimicrobial is successful in maintaining low bacterial levels on a newly placed skin graft until the graft is adequately vascularized, the antimicrobial has contributed to take of the graft.

III. **Review of Labeling**

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

IV. Conclusions and Recommendations

Concerning the clinical study which has already been submitted:

This study concerns comparison of patient records for those who received either a double-antibiotic solution (DAB) containing neomycin sulfate and polymyxin B or DAB plus Sulfamylon Solution 5% (SS5%). There is no protocol-specified assignment of patients to treatment with SS5%. This was a medical decision, made by the attending physician.

The two most relevant endpoints defined in the study were "infectious graft loss" and "treatment failure". Treatment failure combines infectious graft loss with a decision to change topical antimicrobial treatment during the first 5 days of application as a result of infection or colonization. (Note: These decisions regarding infection/colonization were not, in general, based on culture results. Rather, they represent the clinical judgement of the investigator.) The reviewers have added a "treatment switch" endpoint to capture the patients for whom a decision to change topical antimicrobial treatment during the first 5 days of application was made, irrespective of whether graft loss took place.

The reviewers separated the results into patient groups by total body surface area (TBSA) burned. All patients who had burns covering more than 40% TBSA were treated with both SS5% and DAB as well as a variety of topical and systemic antimicrobials. It is impossible to assess the effect of SS5% in this group.

In the 20-40% TBSA burn group, there were a few patients who received DAB alone, but again the confounding effect of concomitant antimicrobials makes the contribution of SS5% difficult to quantify.

However, there are sufficient DAB alone patients in the 0-20% TBSA burn group to permit comparison of the two treatment regimens. In addition, there are a significant number of patients who did not receive concomitant antimicrobials after graft placement. (Note: The following results refer to the patients in the 0-20% TBSA burn group.)

Some patients had multiple grafting procedures. The individual procedures (rather than patients) have been considered in the following tabulation of treatment failure/success.

	Number and % of Procedures with Antimicrobial Failure and Success	
	DAB/SS5% (n* = 100)	DAB alone (n* = 129)
Success	81 (81%)	96 (74%)
Failure	19 (19%)	33 (26%)

* number of procedures in evaluable patients

Treatment switches: In the presentation below, the "Switch" category indicates the number of patients whose therapy was switched from DAB/SS5% or DAB alone in less than 4 days from graft placement because of infection or suspicion of infections. (The surgeon often made these switches without confirmatory cultures.) "Switch to SS5%" indicates the number of patients who were switched from DAB alone to DAB/SS5% because of infection or suspicion of infection. The tabulation concerns number of procedures rather than individual patients.

	DAB/SS5% (n = 100)	DAB alone (n = 129)
Switch	1 (1%)	20 (16%)
Switch to SS5%	0	16 (12%)

One patient failed on both topical medications and was switched to a third before colonization was controlled. However, the remainder of the patients who were switched from DAB alone to DAB/SS5% had successful outcomes.

Finally, it should be noted that all of the patients in this study were in the pediatric age group. It is felt that there is no reason that the effectiveness of Sulfamylon Solution 5% as demonstrated in this age group should not be extrapolated to the populace at large. While there are some data to suggest that patients of advanced age are in general less successful in recovery from burn trauma than younger patients, this lack of success is probably linked to concomitant underlying disease and changing immune function, rather than a difference in response to burn therapy caused by age differences.

SULFAMYLON® For 5% Topical Solution is recommended for approval for the indication "for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds." Sulfamylon cream is currently approved for use in the treatment of second and third degree burns and the proposed indication for the Sufamylon 5% Solution is related. Therefore, data from the study submitted were felt to be adequate to support the proposed indications.

Approval of this application under the conditions of Subpart H of section 314 of the Code of Federal Regulations is being recommended. This Subpart permits approval of drugs used in treating life-threatening illnesses and that provide meaningful benefits over existing treatments. In this regard, the following comments are appropriate:

1. Large total body surface area (TBSA) burns are serious and life-threatening.

2. There is no existing approved treatment for these burn patients who require excision and meshed autografts.

3. Approval under Subpart H also requires that clinical data demonstrate that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or an effect on a clinical endpoint other than survival or irreversible morbidity. SULFAMYLON® For 5% Topical Solution has demonstrated superiority to an unapproved (but commonly used) topical antimicrobial agent in its ability to control bacterial infection when used over meshed autografts. The data support the conclusion that Sulfamylon has an effect that is likely to predict clinical benefit.

4. Approval under Subpart H requires that the applicant perform a Phase 4 study The applicant has agreed to perform a Phase 4 study, which will be designed to the satisfaction of the Agency and the applicant.

/S/

David C. Bostwick, Clinical Reviewer

/S/ 11-28-97

Rosemary Roberts, M.D., Clinical Team Leader

cc: NDA 19-832
HFD-520/Division File
HFD-520/MO/Bostwick + Roberts R
HFD-520/Chem/Timper
HFD-520/Pharm/Ellis
HFD-520/Micro/King
HFD-530/Stat/Yulan Li
HFD-520/Biopharm/Ajayi
HFD-520/DepDir/Gavrilovich
HFD-520/ProjMgr/DillonParker/wp61/sulfa.rev
HFD-340

Concurrence:
HFD-520/ActgDivDir/Chikami 11/28/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

CHEMISTRY REVIEW(S)

Dillon-Parker
520

DEC 1 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 19-832

CHEM.REVIEW Addendum to review #4 **REVIEW DATE: 12/1/97**

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	**2/18/88**	**2/23/88**	**7/11/88**
Amendment	**11/13/90**	**11/19/90**	**5/13/91**
Amendment	**3/27/97**	**3/31/97**	**6/26/97**
Amendment	**6/23/97**	**6/23/97**	**6/26/97**
Correspondence	**10/9/97**	**10/10/97**	**10/16/97**

NAME & ADDRESS OF APPLICANT:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, W VA 26504-4310
(304) 599-2595

DRUG SUBSTANCE NAME

Established: Mafenide acetate, USP
USAN: α-amino-p-toluenesulfonamide monoacetate
Code #: n/a

PHARMACOLOGICAL CATEGORY/INDICATION:

Anti-infective

ROUTE OF ADMINISTRATION: Topical Solution made with 50 gram packet of mafenide acetate, USP, without excipient materials, diluted with 1000 mL of USP Sterile Water for Irrigation or 0.9% Sodium Chloride Irrigation, USP.

Rx/OTC: Rx

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

Mafenide acetate USP; $C_7H_{10}N_2O_2S \cdot C_2H_4O_2$
CAS-13009-99-9

Related documents:

DMF

CONSULTS:

- **Consult for microbiology for the sterilization of the product was sent to HFD-160 on 6/25/97. The sterilization process validation will be submitted and is currently not complete.**
- Environmental Assessment is met by categorical exclusion.
- The EER is acceptable.
- The product will be drug substance, without excipient materials, contained in a bag for a solution. The drug substance testing methodology is prescribed in the USP 23. No method validation is necessary.
- A consult to the labeling committee was found acceptable 8/18/97 for the name "Sulfamylon Powder (Mafenide Acetate, USP)."

REMARKS/COMMENTS:

Mylan amended the NDA 19-832 to provide for sterilization by of the drug product and controls for the process were provided 6/23/97. The validation report has not been provided or completed at this time.

CONCLUSIONS & RECOMMENDATIONS:

Request that an approvable letter issue at this time. The deficiencies noted pertaining to chemistry, manufacturing, and controls are addressed to the firm with regard to sterility assurance. All other aspects with regard to chemistry, manufacturing and controls are acceptable.

/S/ 12/1/97

J. Timper

cc: Org. NDA 19-832
HFD-520/Division File
HFD-520/Katague/Team Leader, Chem DB/C 12-1-97
HFD-520/Timper/Chem 6/26/97
HFD-520/Bostwick/MO
HFD-520/Ellis/Pharm
HFD-520/Sheldon/Micro
HFD-520/Dillon-Parker/CSO
HFC-130/JAllen

HFD 520/Dillon-t.

JUN 27 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 19-832

CHEM.REVIEW #: 3 **REVIEW DATE:** 6/26/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	**2/18/88**	**2/23/88**	**7/11/88**
Amendment	**11/13/90**	**11/19/90**	**5/13/91**
Current review:			
Amendment	**3/27/97**	**3/31/97**	**6/26/97**
Amendment	**6/23/97**	**6/23/97**	**6/26/97**

NAME & ADDRESS OF APPLICANT:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, W VA 26504-4310
(304) 599-2595

DRUG SUBSTANCE NAME

Established: Mafenide acetate, USP
USAN: α-amino-p-toluenesulfonamide monoacetate
Code #: n/a

PHARMACOLOGICAL CATEGORY/INDICATION:

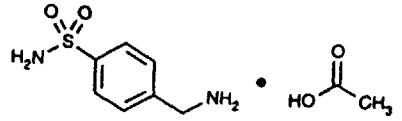
Anti-infective

ROUTE OF ADMINISTRATION: Topical Solution made with 50 gram packet of mafenide acetate, USP, without excipient materials, diluted with 1000 mL of USP Sterile Water for Irrigation or 0.9% Sodium Chloride Irrigation, USP.

Rx/OTC: Rx

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

Mafenide acetate USP, $C_7H_{10}N_2O_2S \cdot C_2H_4O_2$
CAS-13009-99-9



Related documents:

DMF

CONSULTS:

- Consult for microbiology for the sterilization of the product was sent to HFD-160 on 6/25/97.
- Consult for the Environmental Assessment has been forwarded to the EA officer on 6/25/97.
- The EER has been issued with the specified facility for sterilization. The sterilization site is new since 7/23/97. The EER is not complete at this time.
- The product will be drug substance, without excipient materials, contained in a bag for a solution. The drug substance testing methodology is prescribed in the USP 23. No method validation is necessary.
- A consult to the labeling committee has be sent on 6/25/97 for the name "Sulfamylon Powder (Mafenide Acetate, USP)."
- The 2 month stability data for the product sterilized by was provided on 6/23/97. A position on the approvability of the NDA 19-832 is sought from ONDC regarding the lack of stability data.

REMARKS/COMMENTS:

Mylan amended the NDA 19-832 to provide for sterilization by of the drug product and controls for the process were provided 6/23/97. See section above for consults pertaining to evaluation of the sterilization process.

CONCLUSIONS & RECOMMENDATIONS:

Request that a nonapproval letter issue at this time. The deficiencies noted pertaining to chemistry, manufacturing, and controls are addressed to the firm with regard to inspections, stability, sterility assurance.

The DMF for drug substance mafenide acetate, USP, was reviewed at the time of this review and a deficiency letter was issued to DMF Those deficiencies are not considered to be of a serious nature to warrant making the recommendation for that aspect other than approval for NDA 19-832. The reviews of responses to the deficiency letter to that DMF will occur in phase IV.

/S/ 6/26/97

J. Timper

cc: Org. NDA 19-832
HFD-520/Division File
HFD-520/Katague/Team Leader, Chem DBJ 6/27/97
HFD-520/Timper/Chem 6/26/97
HFD-520/Bostwick/MO
HFD-520/Ellis/Pharm
HFD-520/Sheldon/Micro
HFD-520/Dillon-Parker/CSO
HFC-130/JAllen

HFD-520/ Dillon - Parker

APR 24 1998

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
HFD-520

Review of Chemistry, Manufacturing, and Controls

NDA 19-832

CHEM.REVIEW Addendum No. 2 to review #4

REVIEW DATE: 4/23/98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	**2/18/88**	**2/23/88**	**7/11/88**
Amendment	**11/13/90**	**11/19/90**	**5/13/91**
Amendment	**3/27/97**	**3/31/97**	**6/26/97**
Amendment	**6/23/97**	**6/23/97**	**6/26/97**
Correspondence	**10/9/97**	**10/10/97**	**10/16/97**
Correspondence	***1/22/98***	***1/23/98***	***4/23/98***

NAME & ADDRESS OF APPLICANT:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, W VA 26504-4310
(304) 599-2595

DRUG SUBSTANCE NAME

Established:	Mafenide acetate, USP
USAN:	α-amino-p-toluenesulfonamide monoacetate
Code #:	n/a

PHARMACOLOGICAL CATEGORY/INDICATION:

Anti-infective

ROUTE OF ADMINISTRATION: Topical Solution made with 50 gram packet of mafenide acetate, USP, without excipient materials, diluted with 1000 mL of USP Sterile Water for Irrigation or 0.9% Sodium Chloride Irrigation, USP.

Rx/OTC: Rx

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

Mafenide acetate USP, $C_7H_{10}N_2O_2S \cdot C_2H_4O_2$
CAS-13009-99-9

Related documents:

DMF

CONSULTS and ISSUES:

- **The product was agreed to be sterilized by It was found however that the container/closure became unsatisfactory in stability studies. The microbiology review staff agrees that the product can be rendered sterile in a post approval supplement. The product has instructions for filtration at the time of use. The microbiology-CMC staff agreed this would be adequate in the interim with labeling instructions that were prominent. With this provision the product is ready for approval regarding CMC-microbiology concerns. The previous consult to HFD-160, the CMC-microbiology staff, will not be applicable since the subject of that consult will be addressed in the proposed post approval supplement, i.e., to render the product sterile using**

- **A stability update for the product in the packaging to be used not exposed to radiation, the cause of the container/closure failure, is summarized and evaluated in this addendum.**
- **There is a current adequate EER for inspection status for this product.**

REMARKS/COMMENTS:

The microbiologists from HFD-160 have agreed to the items noted above during internal meetings with review staff of NDA 19-832 in HFD-520. Summary of the requested stability data is attached. The firm is granted 18 months expiration dating as noted in the correspondence, the subject of this review.

CONCLUSIONS & RECOMMENDATIONS:

The product can be approved with regard to chemistry, manufacturing, and controls.

/S/ 4/23/98

J. Timper,

cc: Org. NDA 19-832
HFD-520/Division File
HFD-520/Katague/Team Leader, Chem DJK 4/24/98
HFD-520/Timper/Chem 4/23/98
HFD-520/Bostwick/MO
HFD-520/Ellis/Pharm
HFD-520/Sheldon/Micro
HFD-520/Dillon-Parker/CSO
HFC-130/Jallen

Stability data evaluation

The product data supports 18 months expiration dating.

Stability data for 3 lots of the non-sterile product in its current packaging is provided in the current submission. These data provide the results of testing at the following times and conditions:

- 9 months at 40°C/75%RH
- 9 months at 25°C/60%RH
- 9 months at 30°C/60%RH

Additional the FDA has stated to the firm that 18 months expiration data will be granted on the extensive experience with the product and its remarkable excellent stability profile.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

Environmental Assessment

Finding of No Significant Impact

for

NDA 19-832

Sulfamylon Powder for 5% Topical Solution

(mafenide acetate)

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT
NDA 19-832
SULFAMYLON POWDER FOR 5% TOPICAL SOLUTION
(MAFENIDE ACETATE)

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

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

In support of their new drug application for Sulfamylon (mafenide acetate) for 5% Topical Solution, Mylan Pharmaceuticals, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. b(5) [25.31a(b)(3)]

This product has been granted orphan drug designation effective August 29, 1995. The product is for the control of bacterial colonization under moist dressings over meshed autografts on excised burn wounds. See Appendix I of Mylan's attached abbreviated environmental assessment. The product will be used throughout the United States.

The product is a drug that will be used by physicians and other medical personnel to treat burn patients. Its use will be limited to those patients obtaining it upon written prescription of a physician. The administered drug and/or its metabolites will be excreted and will eventually pass through waste water treatment facilities. Used packaging components will be disposed of by hospitals, pharmacies, or the patients in a variety of settings throughout the country, primarily via municipal waste disposal services. These components are comparable in composition and type to packaging components typically used for food products or other medications that already exist in widespread distribution.

The firms which participate in manufacture of the product and the manufacturing sites are as follows:

[redacted] is manufacturer of the pouches located in [redacted]

Mylan Pharmaceuticals Inc., Morgantown, WV is the analytical laboratory and distributor of the dosage form.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

Prepared by: J. Timper, Chemist, HFD-520, 6/25/97

/S/ 6/25/97

Division Concurrence by: David Katague, Ph.D., Team Leader, HFD-520

/S/ 6/25/97

Concurred by: Nancy B. Sager, Team Leader,
Environmental Assessment Team
Office of Pharmaceutical Science, CDER

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

ENVIRONMENTAL ASSESSMENT REVIEW

NDA No. 19-832

Correspondence date	**CDER date**	**Review date**
3/27/97	3/31/97	6/25/97

SUBMISSION TYPE: Resubmission. Original NDA 19-832 submission is dated 2/18/88; major amendment sent on 11/13/90. This is the first Environmental Assessment Review.

REVIEWER: J. Timper

APPLICANT/SPONSOR: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

ASSIGNED DATE: 4/7/97 **COMPLETED DATE:** 6/25/97

DRUG SUBSTANCE NAME

Established:	Mafenide acetate, USP
USAN:	α-amino-p-toluenesulfonamide monoacetate
Code #:	n/a

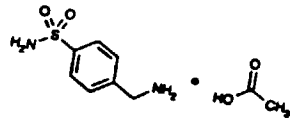
PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-infective

ROUTE OF ADMINISTRATION: Topical Solution made with 50 gram packet of mafenide acetate, USP, without excipient materials, diluted with 1000 mL of USP Sterile Water for Irrigation or 0.9% Sodium Chloride Irrigation, USP.

Rx/OTC: Rx

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

Mafenide acetate USP, $C_7H_{10}N_2O_2S \cdot C_2H_4O_2$
CAS-13009-99-9



Related documents:
DMF

REMARKS:
This product has been granted orphan drug designation effective August 29, 1995. The product is for the control of bacterial colonization under moist dressings over meshed autografts on excised burn wounds. The product will be used throughout the United States.

A second copy of the EA document has been provided by the firm which is adequate for release under Freedom of Information. Both forms of the EA are attached to this review. Their text are the same except for blackened sections in the FOI version.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY/CONCLUSIONS/RECOMMENDATIONS:

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

J. Timper, Chemist, HFD-830

/S/ 6/25/97

cc: Orig: ~~IND~~ NDA 19,832
HFD-520
HFD-520/JMT
HFD-520/Katague DSK 6/25/97
HFD-520/Bostwick/MO
HFD-521/Dillon-Parker/Project Manager

1. **Date: 6/25/97**

2. **Name of Applicant/Petitioner**

Mylan Pharmaceuticals Inc.

3. **Address**

781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. **Description of Proposed Action**

a. **Requested Approval**

NDA 19-832
SULFAMYLON POWDER FOR 5% TOPICAL SOLUTION
(MAFENIDE ACETATE)

b. **Need for Action**

The requested approval is for a NDA which provides for the use of mafenide acetate, USP for the control of bacterial colonization and to prevent infection graft loss when used under moist dressings over meshed autographs on excised burn wounds.

c. **Production Locations**

The firms which participate in manufacture of the product and the manufacturing sites are as follows: is manufacturer of the drug substance located in is manufacturer of the pouches located in Mylan Pharmaceuticals Inc., Morgantown, WV is the analytical laboratory and distributor of the dosage form.

d. **Locations of Use**

The product is a drug that will be used by physicians and other medical personnel to treat burn patients. Its use will be limited to those patients obtaining it upon written prescription of a physician.

e. Disposal Sites

The administered drug and/or its metabolites will be excreted and will eventually pass through waste water treatment facilities. Used packaging components will be disposed of by hospitals, pharmacies, or the patients in a variety of settings throughout the country, primarily via municipal waste disposal services. These components are comparable in composition and type to packaging components typically used for food products or other medications that already exist in widespread distribution.

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

a. Nomenclature

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

Benzenesulfonamide, 4-(aminomethyl)-monoacetate-α-amino-p-toluenesulfonamide monoacetate

ii. Brand/Proprietary Name

Sulfamylon

iii. Chemical Names

(1) Chemical Abstracts (CA) Index Name

Benzenesulfonamide, 4-(aminomethyl)-,monoacetate

(2) Systematic Chemical Name

α-amino-p-toluenesulfonamide monoacetate

b. Chemical Abstracts Service (CAS) registration number

CAS-13009-99-9

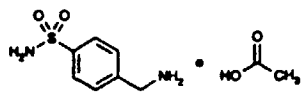
c. Molecular Formula:

$C_7H_{10}N_2O_2S \cdot C_2H_4O_2$

d. Molecular Weight

246.29

e. Structural (graphic) Formula



f. Physical Description

White crystalline powder
Freely soluble in water
See USP 23, Mefenide Acetate, USP

g. Additives

There are no additives in the product, i.e., the product is pure drug substance that is dissolved in sterile water at the time of use.

h. Impurities

The sole known degradant of mafenide acetate is

6. Introduction of Substances into the Environment

a. Substances Expected to be Emitted

1) Bulk drug synthesis

The raw materials used in synthesis are

2) Dosage Form Production

The dosage form is the drug substance put into pouches to be diluted with sterile water at the time of use.

3) Use Sites

The product is a drug that will be used by physicians and other medical personnel to treat burn patients. Its use will be limited to those patients obtaining it upon written prescription of a physician.

4) Disposal Sites

The administered drug and/or its metabolites will be excreted and will eventually pass through waste water treatment facilities. Used packaging components will be disposed of by hospitals, pharmacies, or the patients in a variety of settings throughout the country, primarily via municipal waste disposal services. These components are comparable in composition and type to packaging components typically used for food products or other medications that already exist in widespread distribution.

b. Controls Exercised

Waste water from cleaning the equipment will be discharged into the Morgantown city sewage water treatment system in compliance with Industrial Waste Water discharge Permit No. MUB002. Dust generated during the process will be controlled by the house exhaust. Laboratory waste solvents are handled by a second contractor.

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

disposes of the solvent wastes by incineration and land fill pursuant to their permit EPA#PAD 982567125. This permit was issued by the Federal EPA. Mylan has no contract limits with Envirocure.

Aqueous Emission: the firm provides in the attached EA document, attachment VIII the quarterly monitoring data performed under discharge permit MUB002 and certification of compliance with environmental regulations.

uses incineration as the method of solid waste disposal. Mylan's contract with is in effect.

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

The product is granted orphan drug status so will have low production levels.

e. Expected Introduction Concentrations

The expected introduction of concentrations are within the expected range for the granted orphan drug status.

i. Expected Introduction Concentration from Use (see above)

ii. Expected Introduction Concentration from Disposal (see above)

Items 7 - 11 are not covered in this review following the guidance for preparation of EA of CDER, page 6 "...For infrequent use AEA's, documentation for EA format items 7-11 is ordinarily not required."

7. Fate of Emitted Substances in the Environment
a. Identification of Substance(s) of Interest
b. Physical/Chemical Characterization
i. Water Solubility
ii. Dissociation Constant(s)
iii. Octanol/Water Partition Coefficient
iv. Vapor Pressure or Henry's Law Constant
c. Environmental Depletion Mechanisms
d. Expected Environmental Concentration (EEC)
8. Environmental Effects of Released Substances
9. Use of Resources and Energy
a. Natural Resources and Energy
b. Effect on Endangered or Threatened Species
c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places
10. Mitigation Measures
11. Alternatives to the Proposed Action

12. List of Preparers

13.) Certification: See page 3-242 for certification that the information is true, accurate and complete. The preparer is W. Bradley McMillilen and his signature is found on that page.

14.) References: N/A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

PHARMACOLOGY REVIEW(S)

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

NDA #: 19,832-AZ and BZ

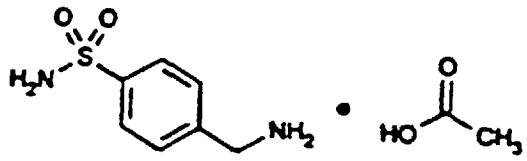
SPONSOR: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

AUTHORIZED REPRESENTATIVE: Frank R. Sisto
Executive Director, Regulatory Affairs

DRUG NAMES: Sulfamylon (Mafenide Acetate) Powder for 5% Topical Solution; α-Amino-p-toluenesulfonamide monoacetate

CATEGORY: sulfonamide antimicrobial

STRUCTURAL FORMULA:



RELATED SUBMISSIONS: NDA 16,763 (Sulfamylon Cream)

NUMBER OF VOLUMES: AZ: 68 (no pharm/tox data, but labeling is in this submission); BZ: 3 (1 for pharm/tox)

CONTAINS INTEGRATED TOX SUMMARY IN LIEU OF FINAL REPORT: No

DATE CDER RECEIVED: 6/30/97

DATE ASSIGNED: 7/15/97 (received desk copy on 7/3/97)

DATE REVIEW STARTED: 8/11/97

DATE 1ST DRAFT COMPLETED: 8/13/97

DATE REVIEW ACCEPTED BY TEAM LEADER: August 13, 1997

REVIEW OBJECTIVES: To determine whether a mouse lymphoma genotoxicity study of Sulfamylon requested by the division was adequately conducted. Results of an adequate genotoxicity study will be included in the label for Sulfamylon.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sulfamylon® Powder for 5% Topical Solution will be supplied as Mafenide Acetate, USP powder in 50 g packets. The label will instruct users that the powder should be constituted with 1000 ml of Sterile Water for Irrigation, USP or 0.9% Sodium Chloride Irrigation, USP , then filtered through a 0.2 μm filter before use.

PROPOSED CLINICAL INDICATIONS: Sulfamylon 5% Topical Solution is indicated for use as a topical antibacterial agent to control bacterial colonization and to prevent graft loss from infection when used under moist dressings over meshed autografts on excised burn wounds.

GENETIC TOXICOLOGY STUDY:

Mutagenicity Test of Sulfamylon Acetate in the TK +/- Mouse Lymphoma Forward Mutation Assay Study No. 18468-0-431)

M.A. Cifone

Report dated 6/25/97, U.S. GLP

BZ: Volume 3, pp. 951-994

Assay:

Results: Sulfamylon did not induce mutations in L5178Y mouse lymphoma cells at concentrations up to 3000 μg/ml in the absence of S-9 or 5000 μg/ml in the presence of S-9.

Mutation Frequency in L5178Y Mouse Lymphoma Cells Treated with Sulfamylon in the Presence and Absence of a Microsomal Activation System

Sulfamylon Concentration (μg/ml)	-S-9		+S-9	
	Relative Growth (% Control)	Mutation Frequency (per 10^6 Cells)	Relative Growth (% Control)	Mutation Frequency (per 10^6 Cells)
Vehicle Control	---	45.8	---	61.8
500	61.3%	47.9	---	---
1000	78.1%	52.3	---	---
1500	53.6%	40.3	---	---
2000	46.2%	60.4	---	---
2500	48.2%	50.6	68.9%	73.0
3000	39.0%	61.2	51.6%	78.3
3500	---	---	63.5%	65.8
4000	---	---	40.4%	78.9
4500	---	---	18.1%	106.9
5000	---	---	9.2%	100.0
MMS, 5 nl/ml	34.7%	537.2	---	---
MMS, 10 nl/ml	10.9%	764.6	---	---
MCA, 2 μg/ml	---	---	25.3%	641.2
MCA, 4 μg/ml	---	---	10.6%	699.6

SUMMARY AND EVALUATION: The sponsor has submitted data from an acceptable mouse lymphoma genotoxicity assay. Sulfamylon did not induce forward mutation of L5178Y TK +/- mouse lymphoma cells, thus it was non-genotoxic in this assay. The results from this study should be included in the appropriate portion of the label for Sulfamylon.

The original pharm/tox review for NDA 19,832 is appended to the current review for use in evaluating some other portions of the Sulfamylon label. The pharmacologist recommends that the data from an approximately 30-year old rabbit teratogenicity study using a subcutaneous route of administration not be included in the label. According to previous reviewers, it was not clear whether the increases in resorptions and skeletal and visceral malformations observed in this study were due to a direct effect on the fetuses or due to maternal toxicity. Subcutaneous injection of Sulfamylon to the pregnant rabbits caused local irritation and necrosis accompanied by inhibition of body weight gain. The subcutaneous route of administration does not appear to have been particularly relevant. Additionally, the dose comparisons for the rat teratology study should be eliminated as the sponsor has not submitted adequate pharmacokinetic data to support them. The pharmacologist also recommends that wording from the sulfonamide class label be added to the Sulfamylon label and that the dose comparison between rats and humans in the Overdosage section be deleted. Recommended wording for the *Carcinogenesis, Mutagenesis, Impairment of Fertility*, *Pregnancy*, and *Overdosage* sections of the label is as follows:

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Pregnancy: Teratogenic Effects. Pregnancy Category C

Overdosage

RECOMMENDATION: The pharmacologist has no objection to the approval of this NDA for Sulfamylon (mafenide acetate) Powder for 5% Topical Solution. The sponsor submitted data from an adequate genotoxicity using mammalian cells as had been requested by the division so that the information could be included in the appropriate section of the label. The

division agreed that the nonclinical data previously submitted for this drug product would be sufficient for supporting this NDA in consideration of Sulfamylon's long history of clinical use and the particular indications being sought for the product. The pharmacologist recommends that the sponsor be asked to modify the label for Sulfamylon as indicated above.

/S/

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Orig. NDA
cc:
HFD-520
HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Ellis
HFD-520/MO/Bostwick
HFD-520/MO Team Ldr/Roberts
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker
HFD-520/Micro/Whiddon

Concurrence Only:
HFD-520/REOsterberg 8/13/97
HFD-520/LGavrilovich 8/15/97

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

NDA #: 19,832-AZ and BZ

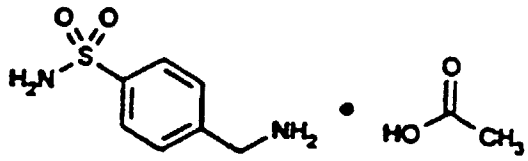
SPONSOR: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

AUTHORIZED REPRESENTATIVE: Frank R. Sisto
Executive Director, Regulatory Affairs

DRUG NAMES: Sulfamylon (Mafenide Acetate) Powder for 5% Topical Solution; α-Amino-p-toluenesulfonamide monoacetate

CATEGORY: sulfonamide antimicrobial

STRUCTURAL FORMULA:



RELATED SUBMISSIONS: NDA 16,763 (Sulfamylon Cream)

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Mutagenicity Test of Sulfamylon Acetate in the TK +/- Mouse Lymphoma Forward Mutation Assay Study No. 18468-0-431)

M.A. Cifone

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BZ: Volume 3, pp. 951-994

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4500	---	---	18.1%	106.9
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SUMMARY AND EVALUATION: The sponsor has submitted data from an acceptable mouse lymphoma genotoxicity assay. Sulfamylon did not induce forward mutation of L5178Y TK +/- mouse lymphoma cells, thus it was non-genotoxic in this assay. The results from this study should be included in the appropriate portion of the label for Sulfamylon.

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Carcinogenesis, Mutagenesis, and Impairment of Fertility

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Overdosage

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division agreed that the nonclinical data previously submitted for this drug product would be sufficient for supporting this NDA in consideration of Sulfamylon's long history of clinical use and the particular indications being sought for the product. The pharmacologist recommends that the sponsor be asked to modify the label for Sulfamylon as indicated above.

/S/

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Concurrence Only:
HFD-520/REOsterberg 8/13/97
HFD-520/LGavrilovich 8/15/97

Orig. NDA
cc:
HFD-520
HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Ellis
HFD-520/MO/Bostwick
HFD-520/MO Team Ldr/Roberts
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker
HFD-520/Micro/Whiddon