CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

STATISTICAL REVIEW(S)

Dillon-Parker
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Statistical Review and Evaluation

NOV 7 1997

NDA#: 19-832

APPLICANT: Mylan Pharmaceuticals, Inc.

NAME OF DRUG: Sulfamylon® Powder for 5% topical Solution (Mafenide Acetate, USP)

INDICATION: 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.

PATIENT POPULATION: Patients with burn wounds

DOCUMENTS REVIEWED: 1.1, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12 (03/27/97)

CLINICAL REVIEWER: HFD-520: David Bostwick

A. Background

This NDA was filed in Feb, 1988 and reviewed. The Agency replied with a non-approvable letter which identifying the deficiencies found, the most critical of which pertained to clinical data. Since the original filing of this NDA, there has been much correspondence and numerous meetings with the Agency to define the clinical data requirements and address all remaining deficiencies. Over time, in an attempt to reach some consensus on an appropriate prospective study design, different types of clinical endpoints (e.g., graft take/loss, microbiology) have been proposed and discussed.

On July 24, 1996, an Advisory Panel of Experts was convened by the Agency to assist in the development of appropriate clinical endpoints which could be used to support marketing approval of Sulfamylon® Powder for 5% topical Solution (SS5%). One conclusion of the Advisory Panel (confirmed with the Agency in Sep., 1996) was that a retrospective review of available safety and effectiveness of SS5% in the treatment of burn wounds could be used to support marketing approval of SS5% NDA 19-832.

Three prospective (non-randomized) studies of burn patients were examined at: University of New Mexico Burn Trauma Unit, NM (safety study), US Army Institute of Surgery at Houston, TX (safety study) and Shriners Burn Institute at Cincinnati, OH (safety and efficacy study). The first study was previously submitted in the non-approved NDA 19-832 and will not be reviewed in the following. The last two are new clinical studies as part of the Amendment to the pending NDA. Based on the discussion with the clinical reviewer, David Bostwick, only the Cincinnati study will be reviewed in this report.

B. Cincinnati Study Report (Protocol 91-02-20-04, INDs

Title: "Use of 5% Mafenide Acetate (Sulfamylon) Solution In Burn Wound Management of Children"

This was a prospective, observational, non-randomized, active controlled clinical evaluation of the clinical benefits and risks of adding SS5% to double-antibiotic solution (DAB) for treatment of grafted burn areas in a clinical setting in which patients with large burns and/or with documented or suspected colonization with Pseudomonas were assigned to treatment with SS5% alternating with using FDA-unapproved but medically accepted topical therapy (DAB) every 2 hours. DAB alone was generally used in patients admitted with smaller burns and no evidence of Pseudomonas colonization.

Patients were treated with topical solutions from the time of wound bed excision through the period of time when the skin grafts became vascularized. The solution treatment period was typically limited to 5 days per graft procedure. Autografts were examined at Days 5, 10, and at the last recorded graft take prior to discharge. A microbial culture was usually obtained prior to excision and grafting and at the Day 2 and Day 5 dressing changes.

The applicant specified the following efficacy endpoints:

- Autograft failure (<85% graft adhesion) due to any cause;
- Autograft failure due to infection;
- Treatment failure (graft failure due to infection or treatment change within the first 5 days of therapy)

The objective of the Investigator-sponsored IND research was to compare graft healing and microbial colonization using DAB with and without the addition of SS5% in acute burn patients.

C. The Applicant's Analysis

The statistical analysis plan was developed during the initiation of data entry and modified during data analysis. The association between the use of SS5% and treatment outcome was assessed by comparing the log odds ratios between the groups using the Cochran-Mantel-Haenszel test stratified by initial burn size. The applicant stated that because of the inherent instability of the odds ratio and the asymptotic confidence interval obtained from the current sample, a bootstrap procedure was used to provide stable and unbiased estimates of the odds ratio and confidence interval.

Patient Characteristics

Four-hundred and thirty-eight (438) patients were evaluable for this study in which 281 were treated with SS5%/DAB and 157 with DAB. Table 1 describes the patient characteristics at admission. Patients were comparable between treatment groups in terms of distributions of age, gender and race. However, there were significant differences among the two groups. Patients in the SS5% group were more extensively burned with more than 50% of burns larger than 20% total burn size area (TBSA) compared with about 10% in the DAB group. The SS5% group also

had a higher incidence of injury due to flame than the DAB group. Hence, patients in the SS5% group were likely to have multiple graft procedures (32% vs 6%) and stayed longer in the hospital (33 days vs 15 days) than the DAB group.

Table 1 Patient Characteristics

	DAB/SS5%	DAB	p-values
# of Treated Patients	281	157	
Age	7.1±0.3	6.4±0.4	0.20
Sex			0.34
male	194	101	
female	87	56	
Race			0.89
Caucasian	221	127	
Black	50	25	
Other	10	5	
Etiology of Burn			<0.001
Flame	196	74	
Scald	73	57	
Chemical	1	2	
Electrical	2	1	
Contact	9	23	
# (%) of Patients by Burn Size			<0.001
0-20%	124 (44%)	140 (89%)	
20-40%	89 (32%)	13 (8%)	
40-60%	38 (13%)	4 (3%)	
>60%	30 (11%)	0 (0%)	
# (%) of Patients by Graft Procedures			0.001
1	193 (68%)	148 (94%)	
>1	88 (32%)	9 (6%)	
3° Burns (%)	23.0±1.3	5.7±0.7	<0.001
Duration of Hospitalization (days)	32.6±1.9	14.9±1.0	<0.001

Efficacy Analysis

The following Table 2 presents the number and percent of patients treated with DAB/SS5% or DAB with autograft failure recorded at Day 5, 10 or at the time of last graft assessment. It can be seen that when all patients studied are considered, the DAB/SS5% patients had a higher graft failure rate. For patients with less 20% TBSA, the differences observed between the two treatment groups favored those patients receiving DAB/SS5%.

Table 2 **Number and Percent of Patients with Autograft Failure**

ime	Cause	All Patients		≤ 20%		>20-40%		>40-60%		>60%	
		SS5%+DAB (n=281)	DAB n=157)	SS5%+ DAB (n=124)	DAB (n=140)	SS5%+ DAB (n=89)	DAB (n=13)	SS5%+ DAB (n=38)	DAB (n=4)	SS5%+ DAB (n=30)	DAB (n=0)
Day 5	All Cause	44 (16%)	11 (7%)	10 (8%)	(9 (6%)	10 (11%)	0	14 (37%)	2 (50%)	10 (33%)	0
	Infectious Cause	24 (9%)	5 (3%)	2 (2%)	3 (2%)	9 (10%)	0	7 (18%)	2 (50%)	6 (20%)	0
	Treatment Failure	28 (10%)	14 (9%)	3 (2%)	11 (8%)	9 (10%)	1 (8%)	9 (24%)	2 (50%)	7 (23%)	0
Day 10	All Cause	63 (22%)	14 (9%)	9 (7%)	12 (9%)	17 (19%)	0	18 (47%)	2 (50%)	19 (63%)	0
	Infectious Cause	38 (14%)	7 (4%)	1 (1%)	5 (4%)	15 (17%)	0	18 (47%)	2 (50%)	19 (63%)	0
	Treatment Failure	41(15%)	16 (10%)	2 (2%)*	13 (9%)	15 (17%)	1 (8%)	13 (34%)	2 (50%)	11 (37%)	0
Last Graft	All Cause	61 (22%)	15 (10%)	10 (8%)	12 (9%)	16 (18%)	0	15 (39%)	3 (75%)	20 (67%)	0
	Infectious Cause	39 (14%)	8 (5%)	2 (2%)	5 (4%)	14 (16%)	0	10 (26%)	3 (75%)	13 (43%)	0
	Treatment Failure	42 (15%)**	17 (11%)	3 (2%)*	13 (9%)	14 (16%)	1 (8%)	11 (29%)	3 (75%)	14 (47%)	0

* Statistically significant at 0.05
** Statistically significant at 0.001

The logit estimator was used to estimate the odds ratio instead of the Mantel-Haenszel estimator (used in the original submission). The applicant indicated that the logit estimator is recommended in the case where the number of strata is small or moderate and the sample sizes within each strata are large (Fleiss, 1981). The 95% confidence intervals for the odds ratios were calculated using the bias-corrected (BC) percentile method (Efron, 1982) based upon 5000 bootstrap samples.

Based on the discussion with David Bostwick, patients with TBSA less than 40% will be focused upon in the following review to assess the difference between the two treatment regimens.

D. The Statistical Reviewer's Comments

1. Study Design

The study was an observational non-randomized controlled clinical evaluation of the clinical benefits and risks of adding SS5% to DAB for treatment of grafted burn areas. Because of the medical decision made by the attending physician, there was no protocol-specified randomized assignment of patients to treatments with either SS5% or DAB. As such, the statistical analysis may be confounded by population characteristics.

2. Bootstrap and Exact Methods for Computing Confidence Interval for Odds Ratios

For constructing confidence intervals for the odds ratio for the stratified 2x2, tables, several methods are available (Fleiss, 1981), such as using various Mantel-Haenszel type chi-square test statistics and the exact method proposed by Gart (1970). The method by Gart is preferred over

the bootstrap method proposed by the applicant in this review mainly because of the following two reasons a and b and comment 3 below.

a) It is an exact test and confidence interval procedure available in software in which the exact CI for the odds ratio can be easily obtained.

b) The bootstrap is a general methodology for assessing statistical accuracy, for example, computing standard errors and confidence intervals. It is particularly useful for situations where full parametric model specification is not made, and for estimators for which it is difficult to compute the standard error otherwise. This is not the case in the present situation.

Since low event rates (especially under 10% among the group of patients with less 20% TBSA) were observed in this study, the variability of the estimate of the odds ratio would be expected to be high. The applicant proposed the bootstrap method and stated that it would provide an unbiased estimate of the odds ratio and stabilize the confidence interval. Such statements are not appropriate. The inherent instability of the sample odds ratio is a result of the sample size and event rate and cannot be addressed by bootstrap method. Hence, the problem of instability of the odds ratio should not be the reason for using the bootstrap method.

3. Misuse of Bootstrap Confidence Interval Procedures

There are several ways of computing confidence intervals using the bootstrap method, such as standard, percentile, student-t, bias-corrected (BC) percentile, etc., each of which has pros and cons. One of the principle goals of bootstrap theory is to produce good confidence intervals automatically. "Good" means that the bootstrap intervals should closely match exact confidence intervals in those situations where statistical theory yields an exact answer, and should give dependably accurate coverage probabilities in all situations. The standard method requires that the sample estimate have a normal distribution with constant variance, and the other approaches require the existence of some monotone transformations which yield a normal distribution. Each method will give a correct CI if the corresponding assumptions are met. Although the standard method is the simplest to use, the BC percentile method might be the better choice if the pivotality condition is met according the above criteria (Efron, 1982). The applicant has tried both methods. However, there are some concerns in the applicant's NDA submission regarding the use of bootstrap method.

a). In their first submission (March 17, 1997), the formula (see below) used for constructing the standard confidence interval for the odds ratio was wrong:

$$\theta\_hat^* \pm t\, S / sqrt(N)$$

where "N" is the number of bootstrap samples; θ_hat^* is the mean of the N bootstrap replicates of the observed Mantel-Haenszel odds ratio denoted as θ_hat, t is 1.96 for 95% confidence interval, "S" is the bootstrap sample standard deviation of θ_hat (i.e., standard error). The correct one should be: $\theta\_hat \pm t\,S$. This implies that the intervals presented are extremely biased in the applicant's favor. Additionally, this formula can be very inaccurate if the assumption of normality with constant variance is not met. The applicant has demonstrated that the odds ratio distribution is not normally distributed. It is bounded by zero and is positively skewed. Hence, the use of the standard method is not appropriate here for computing a CI for the odds ratio.

b). The applicant also used the BC percentile method for computing the CI for the odds ratio in their June 24, 1997 amendment. The confidence interval obtained using the BC percentile method will be exactly correct (in the sense of having exactly the claimed coverage probability) assuming there exists some monotone transformation of θ, say $\phi(\theta)$, so that $[\phi(\theta)-\phi(\theta\_hat)]/\sigma$ is approximately Normal (-z0,1) for some constant σ and z0. Although this assumption is less restricted than the assumption made for the standard method and requires no knowledge of the form of the transformation $\phi(\theta)$, it may not be easily verified. In fact, it is not difficult to see that no monotone mapping $\phi(\theta)$ transforms the family of distributions of the observed odds ratio θ_hat to ϕ. Hence, the use of the BC percentile method is not appropriate here for computing a CI for the odds ratio.

4. Testing for Equal Odds

The applicant used the Chocran M-H chi-square method to test for equal odds ratio between the two groups. This method provides an asymptotic p-value while Gart's test (see Comment 2) gives an exact p-value. In fact, a permutation test based on the M-H test statistic is identical to the Gart's exact test, which can be viewed as a stratified version of Fisher's exact test. The exact method is preferred to the M-H chi-square test when the observed counts (events) are small. The results of Gart's test will be presented in Section E.

5. Adjusting for "Confounding Factors"

For the group of patients with 0-20% TBSA, it is not clear whether the significant benefit from the use of SS5% found from the above analysis is confounded with patient baseline variables, such as etiology of burns and degree of burns, because of the subjective patient selection made by the attending clinicians. Analyses adjusting for patient baseline characteristics will be presented in Section E.

E. The Statistical Reviewer's Analysis

1. Analysis without Adjusting for Baseline Variables

The following tables present the estimated odds ratios for DAB versus SS5%/DAB, their 95% confidence intervals and p-values for testing equal odds ratios using Gart's exact method for patients with 0-40% TBSA. There were 213 patients (124 with 0-20% TBSA and 89 with 20-40% TBSA) in the DAB/SS5% group and 153 (140 with 0-20% TBSA and 13 with 20-40% TBSA) in the DAB group.

In general the confidence intervals are wide, reflecting the variability of the estimate of the odds ratio.

Table 3 presents the exact estimation of odds ratios for patients with 0-40% TBSA burns for All cause Graft Loss, Infectious Graft Loss and Treatment Failure at assessment Days 5, 10 and at the last evaluation prior to discharge. Although the estimated odds of treatment failure for DAB is greater than the odds of treatment failure for SS5%/DAB, no significant odds ratios were observed.

Similarly, Table 4 summarizes the odds ratios for patients with less than 20% TBSA burns. This subgroup of patients may provide a better comparison since the majority of the patients have less than 20% TBSA (124 in the DAB/SS5% group and 140 in the DAB group). In this subgroup, except for the most conservative case (Day 5 All Cause Graft Loss), all odds ratios are in favor of SS5%/DAB (odds ratios are greater than one). However, the only significant odds ratios observed were for treatment failure indicating that the odds of treatment failure for DAB group was significantly greater than the odds of treatment failure for SS5%DAB group at the significance level of 0.05.

Table 3 **Odds Ratio and 95% Confidence Intervals for Patients with 0-40% TBSA**

Time of Assessment	All Cause Graft Loss		Infectious Graft Loss		Treatment Failure	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Day 5	0.64	0.24-1.64	0.67	0.10-3.16	2.52	0.86-7.73
Day 10	0.81	0.34-1.90	0.97	0.24-3.45	2.18	0.84-5.83
Last Graft Assessment	0.77	0.32-1.78	0.85	0.21-2.96	1.98	0.77-5.19

Table 4 **Odds Ratio and 95% Confidence Intervals for Patients with 0-20% TBSA**

Time of Assessment	All Cause Graft Loss		Infectious Graft Loss		Treatment Failure	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Day 5	0.78	0.27-2.23	1.33	0.15-16.22	5.17	1.10-48.96 **p=0.034**
Day 10	1.20	0.44-3.34	4.53	0.50-217.7	6.21	1.26-57.90 **p=0.012**
Last Graft Assessment	1.07	0.41-2.87	2.25	0.36-24.05	4.11	1.09-23.04 **p=0.033**

It should be noted that 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 supportive discharge would be classified as a DAB treatment failure by the analysis. It should be kept in mind that the investigator was aware of treatment assignment at the time of diagnosis. Table 5 presents the distributions of graft failure due to infection vs. change in treatment. It can be seen that the observed significant differences between the two groups for patients with less than 20% TBSA come from the fact that 8 patient initially treated with DAB had switched to other topical treatments while zero (0) patients in the SS5% group had change in treatment during the first five days of therapy. Hence, the observed advantage in treatment failure is primarily the result of differential treatment switching.

Table 5 Distributions of Treatment Failures By Infection and Treatment Change

Time of Assessment	Treatment group	Infectious Graft Loss	Change in Treatment	Treatment Failure
Day 5	DAB	3	8	11
	SS5%	2	2	2
Day 10	DAB	5	8	13
	SS5%	1	1	1
Last Graft Assessment	DAB	5	8	13
	SS5%	2	2	2

2. Analysis Adjusting for Baseline Variables

Since the non-significant results found in Table 4 are comparable to the applicant's analyses with respect to all cause graft loss and infectious graft loss, analyses adjusting for etiology and degree of burn will be performed only using treatment failure.

Table 6 describes the patient characteristics for the group of patients with 0-20% TBSA. Patients were comparable between treatment groups in terms of distributions of age, gender and race. However, the two groups were significantly different with respect to etiology of burns and the degree of burns. Table 7 presents the exact estimations of the odds ratios after adjusting (i.e., stratification) for etiology of burns and degree of burns, respectively. The results indicate that the benefit from the use of SS5% in this subgroup of patients remains after adjustment for etiology of burn and degree of burn, respectively, with respect to treatment failure.

Table 6 Patient Characteristics

	DAB/SS5%	DAB	p-values
# of Treated Patients	124	140	
Age			
Sex			0.32
male	86	89	
female	38	51	
Race			0.55
Caucasian	98	134	
Black	20	22	
Other	6	4	
Etiology of Burn			0.014
Flame	74	61	
Scald	39	53	
Other	11	26	
3° Burns			0.001
< 3°	22	58	
≥ 3°	95	58	
missing value	7	24	

Table 7 **Odds Ratio and 95% Confidence Intervals for Patients with 0-20% TBSA Adjusting for Etiology of Burn and Degree of Burn Using Treatment Failure**

	Etiology of Burn		Degree of Burn	
Time of Assessment	**Odds Ratio**	**95% CI**	**Odds Ratio**	**95% CI**
Day 5	4.64	1.10 - 31.67 **p=0.059**	6.04	1.33 - 43.22 **p=0.03**
Day 10	10.97	1.84 - 241.0 **p=0.0071**	12.96	2.50 - 294.5 **p=0.0054**
Last Assessment	5.36	1.31 - 36.08 **p=0.027**	6.55	1.50 - 45.96 **p=0.017**

F. Overall Summary

The Cincinnati study was reviewed in this report. The applicant used the Cochran-M-H chi-square method (which provided an asymptotic p-value) to test for equal odds ratio between DAB and SS5%. As discussed in this review, Gart's exact method for testing is preferred due to the observed low counts. In addition to the testing of significance, the applicant presented confidence intervals based upon a bootstrap approach. Because of the inappropriate use of bootstrap methods for computing confidence intervals for odds ratios, the confidence intervals for odds ratios provided by the applicant should not be used for assessing the difference between the two groups. Exact confidence intervals based on the Gart's test procedure were presented in this review.

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. However, it is unknown whether this association reflects the benefit of adding SS5% to DAB or is the result of non-random treatment assignment and investigator knowledge of treatment at the time treatment failure was assessed. The additional benefit of adding SS5% to DAB with respect to graft loss was not statistically established.

11/7/97

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Mathematical Statistician

cc: Paul Flyer, Ph.D. PF 11/7/97
Statisticial Team Leader

Archival NDA #19-832
HFD-520
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HFD-520/Dr. R. Roberts
HFD-520/Ms. Dillon-Parker
HFD-725/Dr. Flyer
HFD-725/Dr. Lin
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This review contains 10 pages.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERNDA 19-832

MICROBIOLOGY REVIEW(S)

HFD 510 Dillion-Parker
JUL 10 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 19-832 **REVIEW #:** 01 **REVIEW DATE:** 10-Jun-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AZ/Major Amendment	27-Mar-97	31-Mar-97	17-Feb-97

NAME & ADDRESS OF APPLICANT: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26505

DRUG PRODUCT NAME

Proprietary:	Sulfamylon
Nonproprietary/USAN:	Mafenide Acetate, USP
Code Names/#'s:	
Chemical Type/:	

PHARMACOLOGICAL CATEGORY/INDICATION:	Topical, for burns
DOSAGE FORM:	5% topical solution
STRENGTHS:	5%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	XX **Rx** _____ **OTC**

USP Dictionary of USAN and International Drug Names. 1995. Carolyn A. Fleegler ed. Page 416.

RELATED DOCUMENTS: IND#s

REMARKS/COMMENTS:

TABLE OF CONTENTS

INTRODUCTION

The sponsor is presenting the results of a retrospective study done by Glenn D. Warden, MD, of Shriners Burns Institute, 3229 Burnet Avenue, Cincinnati, OH 45229-3095. The objective of this research was to compare graft healing and microbial colonization using FDA-unapproved, but medically accepted topical therapy with and without the addition of SS5% (the study drug - Sulfamylon 5% topical solution)with wounds requiring re-grafting. A subset of the research population consisted of children with acute burns which were treated with autografts. The submitted reports focused on the clinical and microbial results for autograft procedures treated with double-antibiotic solution (neomycin sulfate 40 mg/polymixin B 200,000 units per liter [hereinafter termed **DAB**]) every two hours with or without alternating therapy with 5% mafenide acetate (Sulfamylon Powder for 5% topical solution [hereinafter termed **SS5%**]) solution to prevent infection on excised burn wounds requiring autografts in children treated at the Shriners Burns Institute.

Objectives:

The study goal was to compare the safety and efficacy 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.

Study Design:

This study was a retrospective non-randomized controlled clinical evaluation of the clinical benefits and risks of adding SS5% to DAB for treatment of grafted burn areas in a clinical setting in which patients with large burns and/or with documented or suspected colonization with *Pseudomonas* were assigned to treatment with SS5% alternating with DAB every 2 hours. DAB alone was generally used in patients admitted with smaller burns and no evidence of *Pseudomonas* colonization.

The topical agents were used to prevent bacterial colonization of burn wounds with two primary goals:

1. Prevention of invasive infection.
2. Prevention of infectious graft loss.

The 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. 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.). After autograft vascularization (approximately five days after grafting) the type of dressing was changed from wet to dry. 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. The use of ointment or cream preparations was justified at this time because they could be safely applied over the vascularized graft without danger of mechanical disruption. This change in the type of treatment was considered to be a normal progression in the care of the wounds and was performed to prevent infection or maceration of the graft tissue. The "dry" sterile dressing was continued until graft margins were healed.

The choice of perioperative topical therapy proceeded according to the medical judgment of the prescribing physician. Loss of an autograft in these critically ill patients could be life-threatening. Thus, if a graft became

colonized or infected, antimicrobial therapy was changed to an antimicrobial solution or cream known to be effective against the colonizing organism(s). Revisions in initial therapy may have involved adding additional agents or changing to an entirely new treatment regimen.

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.

Endpoints (Assessment of Autograft Take and Loss)

The focus of the analysis was to examine the incremental effects of SS5% on the outcome of autograft procedures treated with DAB. For the purpose of analysis, "graft loss" is defined as autograft adhesion to the wound bed of less than 85% on any graft procedure. In other words, if less than 15% of the total autograft area during a procedure failed to attach to the wound bed, the autograft procedure was considered to be a failure. The four most common reasons for graft loss are:

1. Mechanical disruption
2. Hematoma/seroma beneath the graft.
3. Poor base (depth of injury).
4. Infection.

The goal of effective topical antimicrobial therapy was to prevent autograft loss due to infection. Thus, three endpoints have been defined for evaluation of autograft take and loss:

1. ***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 DMB. 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.

2. ***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.

3. ***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.

Loss of an autograft in children critically ill from burn wounds can be life-threatening. At the first sign of a threat to the graft, the attending physician took all possible steps to salvage the autograft. This is especially true if there was any evidence of signs of colonization, impending or frank infection. As a result, the combination of *Infectious Graft Loss* or changes in therapy to prevent *Infectious Graft Loss* was an important consideration for the evaluation of topical antimicrobial effectiveness. Since *Infectious Graft Loss* is already captured, this endpoint essentially adds (as failures) patients who required infection-related changes in topical antimicrobial therapy to save the autograft.

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.

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 becomes 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 Burns 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).

Microbial/Fungal Prevalence

Microbial growth was determined through wound cultures obtained at different times throughout a patient's hospitalization (most commonly, prior to excision and grafting, at days 2 and 5 after grafting, and thereafter under suspicion of infection). Prevalence of microbial colonization was defined as the number of individuals with at least one positive culture during a fixed time period immediately prior to the first autograft procedure (defined as Day 0 for presentation purposes). Days of particular interest were represented by the following ranges: 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). Assessment of microbial colonization was described as any growth, and by specific organisms. The microbial categories were defined as follows:

Any growth: growth of any of any microorganisms.

Staphylococcus spp.: *Staph. aureus,* coagulase negative *Staph.*, and methicillin-resistant *Staph. aureus.*

Pseudomonas and *Xanthomonas* spp.: *Pseudomonas* and *Xanthomonas*

Gram-positive organisms: *Staph. aureus,* coagulase negative *Staph.*, *Streptococcus,* methicillin-resistant *Staph. aureus,* and Group D *non-Enterococci.*

Gram-negative organisms: *Pseudomonas* species, *E. coli, Klebsiella, Enterobacter, Proteus, Enterococcus, Xanthomonas* species, *Serratia marcescens, Aeromonas,* Gram-negative rods, *Providencia rettgeri, Morganella morganii, Serratia liquefaciens, Neisseria,* and *Serratia plymuthica.*

Any fungus: *Candida,* yeast, and fungus or mucor.

Of particular interest was microbial prevalence data for Days 3 - 5, since this represented the time that topical solution was discontinued in the majority of the uncomplicated burn wounds. The p-values (by the Fisher's Exact test) can be interpreted as evidence of treatment effectiveness since, with respect to exposure of a patient to microbes, the patients can be considered to have presented to the hospital randomly.

Microbial Cultures

Surface cultures (swabs) were routinely obtained from graft sites to monitor for colonization. A culture was usually obtained prior to excision and grafting and at the Day 2 and Day 5 dressing changes. Additional cultures were obtained when clinically indicated. Semi-quantitative surface cultures were taken when appearance and/or odor indicated the possibility of invasive infection. Swabs were transported to the Microbiology lab in culture tubes containing Stuart's transport medium. Samples were plated onto blood agar (non-selective), eosin-methylene blue agar (selective for gram negatives), and phenylethyl alcohol agar (selective for gram positives). Swabs were then placed in thioglycolate broth. Identification from pure culture was made using the Vitek system. Results were reported either in terms of organism grown or in semi-quantitataive terms according to the following:

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

A summary of microbial prevalence on burn wounds over time for all patients receiving DAB/SS5% and DAB alone is displayed in Table 1 (shown following).

Compared to patients on DAB alone, patients receiving DAB/SS5% had fewer wound cultures with any growth ($p = 0.001$ at Day 5), a lower prevalence of all gram negative organisms ($p \leq 0.001$ at Days 5 and 10), less wound cultures detecting *Pseudomonas* and *Xanthomonas* organisms ($p < 0.001$ at Day 5), and a reduced prevalence of *Staphylococcus* or gram positive organisms at Day 5 ($p \leq 0.05$). Consistent with the larger and more severe burn wounds in the DA3/SS5%, fungal prevalence was greater in patients receiving DAB/SS5% when compared to that recorded for children receiving DAB alone ($p < 0.01$ for Days 2 and 5). Thus, the combination of DAB/SS5% controlled bacterial proliferation more effectively than DAB alone.

Table 1. Microbial Prevalence in Wound Cultures by Organism for All Patients

Organism	Day from Day 0	DAB	SS5% / DAB	p-value	Relative Increase DAB/SS5%/DAB
Any Growth	0	n=66 43.9%	53.9% n=204	0.202	
	2	n=78 46.2%	53.2% n=190	0.347	403.42
	5	n=76 76.3%	56.9% n=181	**0.005**	1326.01
	10	n=16 87.5%	64.2% n=106	0.087	519.72
Pseudomonas &	0	n=66 7.6%	10.3% n=204	0.635	
Xanthomonas spp.	2	n=78 14.1%	16.8% n=190	0.715	135.53
	5	n=76 48.7%	16.6% n=181	**<0.001**	884.15
	10	n=16 43.8%	25.5% n=106	0.143	322.77
Staph. Spp.	0	n=66 31.8%	30.4% n=204	0.878	
	2	n=78 16.7%	12.1 % n=190	0.329	78.88
	5	n=76 25.0%	14.4% n=181	**0.048**	40.63
	10	n=16 31.3%	22.6% n=106	0.529	6.1 3
Gram (+)	0	n=66 33.3%	35.8% n=204	0.768	
organisms	2	n=78 19.2%	13.2% n=190	0.257	67.07
	5	n=76 27.6%	14.9% n=181	**0.022**	29.32
	10	n=16 31.3%	22.6% n=1O6	0.529	16.29
Gram (-)	0	n=66 18.2%	31.4% n=204	0.041	
organisms	2	n=78 23.1%	34.7% n=190	0.081	256.18
	5	n=76 61.8%	35.9% n=181	**<0.001**	I 671.60
	10	n=16 81.3%	38.7% n=106	0.002	I 491.30
Fungus	0	n=66 1.5%	4.9% n=204	0.304	
	2	n=78 5.1%	16.8% n=190	**0.010**	98.82
	5	n=76 4.0%	23.8% n=181	**<0.001**	43.21
	10	n=16 12.5%	31.1 % n=106	0.150	137.15

Any growth: growth of any of any microorganisms.
Staphylococcus spp.: *Staph. aureus*, coagulase negative *Staph.*, and methicillin-resistant *StaPh. aureus*.
Pseudomonas and *Xanthomonas* spp.: *Pseudomonas* and *Xanthomonas*
Gram-positive organisms: *Staph. aureus*, coagulase negative *Staph.*, *Streptococcus*, methicillin-resistant *Staph. aureus*, and Group D *non-Enterococci*.
Gram-negative organisms: *Pseudomonas* species, *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*, Enterococcus, *Xanthomonas* species, *Serratia marcescens*, *Aeromonas*, Gram-negative rods, *Providencia rettgeri*, *Morganella morganii*, *Serratia liquefaciens*, *Neisseria*, and *Serratia plymuthica*.
Any fungus: *Candida*, yeast, and fungus or mucor.

Package Insert.

Mafenide acetate exerts a bacteriostatic action against gram negative and gram-positive organisms, including *Pseudomonas aeruginosa* and some strains of anaerobes. The agent is expected to be active against clinical isolates at 50 mg/ml or less which is the surface concentration of constituted drug when applied topically. The following *in-vitro* data are available but their clinical significance is unknown.

Organism	**MIC 50% (mg/ml)**	**MIC 90% (mg/ml)**
Pseudomonas aeruginosa	12.5	25
Klebsiella pneumoniae	25	25
Enterobacter cloacae	12.5	25
Escherichia coli	12.5	25
Staphylococcus aureus	6.3	12.5

CONCLUSIONS & RECOMMENDATIONS:
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.

/S/

Robert G. Whiddon, Ph.D.
Review Microbiologist

cc: Orig. NDA 19-832
cc: Orig. NDA
HFD-520 Division File
HFD-520/Micro/Whiddon
HFD-520/MO/Bostwick
HFD-520/Pharm/Adeyemo
HFD-520/Chem/Rou
HFD-520/CSO/Dillon-Parker
Filename: **N19832W2.DOC**

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/GLMicro/ATSheldon
RD init 6/18/97 ATS
7/15/97
7/10/97

JUL 7 1997

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1
7 July 1997

A. 1. NDA 19-832

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

2. PRODUCT NAMES: Sulfamylon® (mafenide acetate, USP) Powder for 5% Topical Solution

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Powder for topical solution.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product 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.

B. 1. DATE OF INITIAL SUBMISSION: 19 February 1988

2. DATE OF AMENDMENT: 23 June 1997 (Subject of this review.)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 27 June 1997

C. REMARKS: The amendment is a response to the reviewing division's 7 May 1997 telefax containing chemistry questions. The 7 May response was a response to an 27 March 1997 amendment to the NDA containing a revised CMC section. The applicant has been requested to render this product sterile.

The finished packaged product is sterilized by:

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns.

/S/

7 July 1997

Paul Stinavage, Ph.D.

cc: Original NDA 19-832
HFD-520/J. Timper/M.P. Dillon-Parker/D. Bostwick
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 7 July 1997
R/D initialed by P. Cooney D. Thurso for PHC

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW ~~#1~~ #2
3 October 1997

JMT 11/20/97

A. 1. NDA 19-832

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

2. PRODUCT NAMES: Sulfamylon® (mafenide acetate, USP) Powder for 5% Topical Solution

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Powder for topical solution.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product 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.

B. 1. DATE OF INITIAL SUBMISSION: 19 February 1988

2. DATE OF AMENDMENT: 29 August 1997 (Subject of this review.)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 16 September 1997

C. REMARKS: The amendment is a response to the reviewing division's 7 May 1997 telefax containing chemistry questions. The 7 May response was a response to an 27 March 1997 amendment to the NDA containing a revised CMC section. The applicant has been requested to render this product sterile.

The finished packaged product is sterilized by:

The review chemist should examine the temperature range indicated by "refrigerated" storage conditions for the reconstituted solution to determine that they are appropriate for use with this product.

D. CONCLUSIONS: The application is not approvable from the standpoint of product quality microbiology. The efficacy of the sterilization process and the ability of the container/closure system to maintain product sterility have not been demonstrated.

/S/

3 Oct 1997

Paul Stinavage, Ph.D.

Date 10/3/97

cc: Original NDA 19-832
HFD-520/J. Timper/M.P. Dillon-Parker/D. Bostwick/D. Katague
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 3 October 1997
R/D initialed by P. Cooney

T. Mayer
520

NOV 3 1997

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #3
3 November 1997

A. 1. NDA 19-832

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

2. PRODUCT NAMES: Sulfamylon® (mafenide acetate, USP) Powder for 5% Topical Solution

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Powder for topical solution.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product 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.

B. 1. DATE OF INITIAL SUBMISSION: 19 February 1988

2. DATE OF AMENDMENT: 28 October 1997 (Subject of this review.)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 31 October 1997

C. REMARKS: The amendment is a response to the reviewing division's facsimile correspondence dated 21 October 1997 and a follow-up clarification provided from the Agency on 23 October 1997 concerning the comment's contained in Microbiologist's Review #2 dated 3 October 1997.

The finished packaged product is sterilized by:

D. CONCLUSIONS: 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.

/S/

3 November 1997

Paul Stinavage, Ph.D.

11/3/97

cc: Original NDA 19-832
HFD-520/J. Timper/M.P. Dillon-Parker/D. Bostwick/D. Katague
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 3 November 1997
R/D initialed by P. Cooney

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19-832

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 19,832 **SUBMISSION DATE:** July 25, 1997
SULFAMYLON®
(Mafenide acetate, powder for 5% topical solution)

Mylan Pharmaceuticals Inc. **REVIEWER:** Funmilayo O. Ajayi, Ph.D.
781 Chestnut Ridge Road
Morgantown, West Virginia 26504 **TYPE OF SUBMISSION:** Original NDA

BACKGROUND: This submission seeks approval for Mafenide acetate, powder for 5% topical solution for use in burn patients. There was no Pharmacokinetics study but the sponsor provided information from literature article regarding the extent of systemic absorption following topical application of this agent to burned skin. The sponsor request a waiver of the need to demonstrate systemic bioavailability for this product.

FINDINGS: Three articles were found during a literature search on the subject matter (White & Asch (1971), N.E.J.M. 284:1281-1286 - Reference 1; Harrison *et.al.* (1972), J. Trauma 12:994-998 - Reference 2; Harrison *et.al.* (1971), Arch. Surg. 103:449-453 - Reference 3). In general, the peak concentration of mafenide acetate in the excised human skin was 1.25 mg/100 mg tissue following application of 5% sulfamylon solution. The concentrations of the drug over the wound were 5.5-6.3% at 3h and 5.9% at 4 h following application. Discussions with the reviewing medical officer revealed no safety concern for this product. The summary of each article can be found in the Attachments.

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

/S/ 10/28/97
Funmilayo O. Ajayi, Ph.D.
Div. of Pharmaceutical Evaluation III

FT initialed by Frank Pelsor, PharmD..... /S/ 10/28/97

N 19832
cc: HFD-520 (Clinical Division)
HFD-880 (DPE3, Pelsor, Ajayi,)
CDR (Attn: B. Murphy)

ATTACHMENTS

REFERENCE 1

ACID-BASE EFFECTS OF TOPICAL MAFENIDE ACETATE IN THE BURNED PATIENT

M. White and M. Asch described acid-base effects of topical mafenide acetate in the burned patients. Only the absorption section of the paper will be summarized in this discussion.

Method

Ten (8 males and 2 females, age 18 to 48) injured patients with thermal burns admitted to the Institute of Surgical Research were studied within 48 hours of injury. The patients each received a single application of 11.2 % mafenide acetate cream, ranging from 125 to 675 g (Table 2), or a dose of 14 to 77 g of mafenide acetate. Each subject's burned area ranged from 15% to 57% of total body surface for second degree burns and ranged from 0% to 58% of total body surface for the third degree burns (Table 2). Blood samples were taken at pre-dose application, and at 1, 2, 3, 4, 8, 12 and 24 hours following 11.2% mafenide acetate cream application. In vivo mafenide acetate is converted to p-carboxybezenesulfonamide, PCBS. Thus, both blood levels of mafenide (MA) and PCBS were determined photofluorometrically from a protein free filtrate of blood.

Results

The blood levels of the drug rose rapidly after topical application, peaking at the second hour ranging from μg/mL, whereas the PCBS levels peaked at the third hour ranging from μg/mL. The combined MA and PCBS levels were plotted by the authors as shown in Figure 1 of reference 1. Blood levels had fallen to pre-treatment levels twenty-four hours after the application. The individual peak blood drug levels and peak blood PCBS levels are also displayed in Table 2.

Table 2. Size of Burn, Dose of MA Applied and Peak Blood Levels of MA and PCBS

Patient No.	Total body surface burn (%)		Dose	Peak (mmole/L)	
	2nd degree	3rd degree	(g of cream)	MA	PCBS
	55	4	654	0.52	0.35
	31	2	353	0.31	0.10
	49	13	130	0.36	0.20
	25	10	125	0.19	0.05
	44	0	410	0.90	0.50
	15	58	280	0.21	0.15
	29	38	423	0.44	0.30
	31	20	675	1.06	1.69
	19	39	685	0.63	0.45
	57	12	460	0.95	0.45

Retrieved from Table 1 of Reference 1

The data indicated that topically applied MA was systemically absorbed when the area of total body surface involved and the dose necessary to cover the area were large. The data also showed that absorption of MA was rapid with peak levels occurring from the first to the third hours following MA cream application. The absorbed MA was rapidly deaminated to PCBS.

REFERENCE 2

THE ABSORPTION INTO BURNED SKIN OF SULFAMYLON ACETATE FROM 5 PERCENT AQUEOUS SOLUTION

The objective of the study, which was conducted by H. Harrison et. al. at Rochester Medical Center, was to estimate the absorption of sulfamylon into human and rat burned skin following 5% sulfamylon solution application.

Method

Fourteen grams of 5% aqueous sulfamylon acetate solution was placed on a 70 cm^2 section of the 24-layer gauze burn dressing. Sprague rats (200 g) were scald-burned for 10 seconds at 95° C following anesthesia. The rats were depilated for 20 minutes, the proteo-lipid layer removed, and the rats were placed on a balance. Evaporation from the animal plus burn dressing was determined by hourly weight loss measurements. The respiratory portion was measured in the unburned rat without the wet dressing. The evaporation rate for sulfamylon solution was then computed by subtracting the respiratory component from the hourly measured loss.

Fifty μL samples of the sulfamylon solution was taken from the soak at hourly intervals 0-5 hours after application and the concentration of sulfamylon from the soak was determined. The percentage of the dose delivered to the wound was calculated using the changes in fluid weight and sulfamylon concentration in that fluid at each sampling time following application.

The amount of sulfamylon measured was expressed as mg per 100 mg tissue. Additionally, burned skin was removed from patients at the time of major debridement before grafting. Then the human burned skin replaced an excised rat burned skin on the backs of rats. Hourly tissue biopsies of full-thickness skin were taken from human and rat burned skin. Absorption of the drug on both human and rat skin sites were carried out simultaneously.

Results

The concentration change over the wound was slight during the initial 4 hour period. The concentrations were constant ranging from % at hour and % at hour. The concentration increased only % while the fluid evaporated completely at 5 hour, indicating sulfamylon absorption into the burn wound. The dose delivered in the wound can be estimated through the data of the loss of aqueous carrier and the concentrations at each time point. Over the 4-hour period following application, approximately 81.5% of the dose was delivered from the soak to the tissue. The amount of drug delivered to the wound was 0.24-0.40 $g/kg/hr/m^2$.

As shown in Figure 1 of reference 2, sulfamylon concentrations (in mg per 100 mg tissue) for the excised human skin and the in-place rat skin were similar. Peak drug concentrations were 1.25 mg/100mg tissue for human skin and 1.0 mg/100 mg tissue for rat skin, respectively. The time to reach peak sulfamylon concentration was 4 hours after application. The peak concentration following the 5% cream application was about half that following the 5% solution application.

REFERENCE 3

THE BEHAVIOR OF MAFENIDE ACETATE AS A BASIS FOR ITS CLINICAL USE

The first objective of the study was to estimate the rate of delivery of sulfamylon cream to the wound using excised human burned tissue placed on the scald-burned rat skin. The second objective was to determine the route and rate of excretion following intravenous sulfamylon injection in rats. The study was conducted by H. Harrison et. al. at Rochester Medical Center.

Method

Human burned tissue was excised and was placed on the back of a rat with burned skin. Tissue biopsies were performed from 5 minutes to 24 hours following 5% and 11.2 % ^{14}C-sulfamylon cream application. The concentrations of the drug were determined in the burned skin tissue. Time course for the drop in drug concentration from its carrier cream was determined. Subsequently, the percentage of the dose delivered was estimated.

Excretion studies were done following intravenous injection of 1 micro curie of ^{14}C-sulfamylon (1 mg of the drug) in rats. Serial kidney, liver, plasma, and heart muscle tissue samples were taken post injection to determine the radioactivity levels.

Results

As shown in Figure 2 of reference 3, 55% of the dose had been estimated to deliver to the wound one hour following drug application, and 88% after five hours. Figure 4 of the reference showed the changes in concentration of ^{14}C-mafenide versus time in burned tissue following 5% and 11.2% cream application. The peak concentrations were 0.6 mg/100mg and 1.1 mg/100mg for 5% and 11.2 % cream, respectively. The time to peak was about 2 hours post application.

Figures 6 to 8 of the reference 3 presented the elimination profiles of the drug in rat kidney, liver, plasma and heart muscle tissues following ^{14}C- sulfamylon intravenous injection. The initial kidney radioactivity levels were the highest, 6.9 times the liver and the heart radioactivity levels, and 18 times the plasma levels. The half-life, 10 to 15 minutes, was similar in these tissues. Urinary radioactivities returned to background levels 48 hours following injection. Eventually, 80% of the dose was recovered in the urine. No organ residuals were detectable six days after injection.

CONCLUSIONS

- The concentration change over the wound was slight during the initial 4 hours following 5% sulfamylon solution application. The concentrations were constant ranging from % % at hours and % at hours post application.

- After sulfamylon solution application, the concentration increased only % while the fluid evaporated completely at hours, indicating sulfamylon absorption into the burn wound.

- Over the initial 4 hours following either 5% sulfamylon solution or sulfamylon cream application, approximately 80% of the dose was estimated to deliver from the soak to the tissue.

- The peak drug concentrations were 1.25 mg/100mg human burned skin tissue following 5% solution application and 1.1 mg/100mg human burned skin tissue following 11.2 % cream application, respectively. The concentration versus time profiles were similar except that time to peak for the solution application was 4 hours post application and that for the cream was 2 hours post application.

- The blood drug levels rose rapidly following 11.2% sulfamylon cream application, peaking at the second hour, ranging from μg/mL. When the area of total body surface involved and the dose necessary to cover the burned area were large, the topically applied sulfamylon was systemically absorbed.

- The total radioactivity levels versus time profiles in kidney, liver, plasma, and heart muscle tissues were studied in rats following 1 mg ^{14}C-sulfamylon intravenous injection. The half-life, 10 to 15 minutes, was similar in these tissues. The initial radioactivity levels ranked in the following order: kidney, liver, heart, and plasma. Eighty percent of the dose was recovered in the urine. No organ residuals were detectable six days following injection.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

ADMINISTRATIVE DOCUMENTS

SULFAMYLON[R] 5% SOLUTION
(MAFENIDE ACETATE 5% SOLUTION)

PATENT CERTIFICATION

Sulfamylon[R] Cream NDA 16-763

U.S. PATENT No. 3497599

ISSUED: February 24, 1970

EXPIRED: February 24, 1987

Patent coverage for this product has expired.

C7

EXCLUSIVITY SUMMARY for NDA # 19-832 SUPPL # —

Trade Name Sulfamylon for 5% Topical Solution **Generic Name** mafenide acetate

Applicant Name Mylan Pharmaceuticals Inc. **HFD-**520

Approval Date 6-5-98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

   If yes, what type? (SE1, SE2, etc.) —

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   not applicable

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   not applicable

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /__/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16-763 Sulfamylon Cream

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____
_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /X/

If yes, explain: _____
_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /X/

If yes, explain: _____
_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 91-02-20-04 (Dr. Warden)

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # 91-02-20-01 (Dr-Waider)

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /__/ ! NO /X/ Explain: ____

! _____

Investigation #2 !

IND # ____ YES /__/ ! NO /__/ Explain: ____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /X/ Explain _____ ! NO /__/ Explain _____

Sponsor Supplied ! _____

study drug. ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____

/S/

_____ 11/24/97

Signature Date

Title: Project Manager

/S/

_____ 11/25/97

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 19-832 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 520 Trade and generic names/dosage form: Sulfamylon Powder for 5% Topical Solution (mafenide acetate) Action: (AP) AE NA

Applicant Mylan Pharmaceuticals Therapeutic Class 3S 4020190 Topical Antimicrobial

Indication(s) previously approved N/A

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

Indication in this application for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds (For supplemen answer the following questions in relation to the proposed indication.)

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

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

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

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

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

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

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

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

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

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

/S/ 5/27/98
Signature of Preparer and Title Date

cc: Orig (NDA)/PLA/PMA # 19-832
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/~~SOImstead~~ (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

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

/S/ May 28, 1998
Medical Officer Date

/S/ 6/2/98
Division Director Date

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/~~PLA~~/~~PMA~~ # 19-832 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Sulfamylon Powder for 5% Topical Solution (mafenide acetate) Action: AP (AE) NA

Applicant Mylan Pharmaceuticals Inc. Therapeutic Class Topical

Indication(s) previously approved N/A

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

Indication in this application for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under appropriate dressings over meshed autografts on excised burn wounds. (For supplements, answer the following questions in relation to the proposed indication.)

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

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

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

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

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

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

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

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

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

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

/S/ Rajni Mgr — November 25, 1997

Signature of Preparer and Title — Date

cc: Orig (NDA)/PLA/PMA # 19-832
HFD-520 /Div File
(NDA/~~PLA~~ Action Package)
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/12/96)

Consult #834 (HFD-520)

SULFAMYLON mafenide acetate powder for topical solution

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name. However, the Committee feels the proper established name for this product is mafenide acetate for topical solution. Powder is no longer included in USP monograph titles.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 8/18/97, Chair
CDER Labeling and Nomenclature Committee

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 12, 1997

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

Attention: Frank R. Sisto
Executive Director, Regulatory Affairs

Dear Mr. Sisto:

Reference is made to your designated orphan product submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for mafenide acetate solution (Sulfamylon®) (application #90-478).

We also refer to your December 9, 1997 submission in which you requested to amend your designated indication to coincide with the proposed marketing indication.

We have completed our review of your submission. The revised designated indication for mafenide acetate solution is for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds.

If you need further assistance or have additional questions, please feel free to contact Ms. Erica McNeilly at (301) 827-0983.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

cc:
HFD-85/M.A.Holovac
HFD-520/M.Dillon-Parker
HF-35/OP File #90-478
HF-35/chron
HF-35/EKMcNeilly 12/12/97 amend478.wpd

NDA 19-832

JUL 31 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 pending March 31, 1997 new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulfamylon® (mafenide acetate, USP) Powder for 5% Topical Solution.

We also refer to your amendment dated June 23, 1997.

To complete our review of the methods of sterilization section of your submission, we request the following:

1. Concerning validation of the sterilization of the product the following information should be submitted:

   a. The Process

   b. The Packaging of the Product

      The packaging of the product within the shipping carton and within the carrier should be described.

   c. Dose Mapping Studies

      Dose mapping studies for identification of low and high dose sites and demonstration of uniformity and reproducibility of the process should be described.

d. Microbiological Methods and Controls

The microbiological method and controls used to establish, validate, and audit the efficacy of the cycle should be described.

e. Monitoring Stability

The program for monitoring the stability of the packaging and the microbial integrity of the container-closure system barrier over the claimed shelf life should be described.

2. Concerning the storage of the prepared solution:

A seven day holding time for a sterile solution is lengthy. The labeling should specify storage conditions. The storage time for the prepared solution should be validated or reduced.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

Sincerely yours,

/S/

David B. Katague, Ph.D.
Team Leader, Chemistry
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 19-832
HFD-520/Div. Files
HFD-520/PMS/M.Dillon-Parker
HFD-520/TLClin/Roberts
HFD-520/Clin/Bostwick
HFD-830/Chem/Timper JMT 7/31/97
HFD-830/TLChem/Katague
HFD-805/Consult file/Stinavage
HFD-830/ONDC Division Director (only for CMC related issues)

Drafted by: mdp/July 30, 1997/NDAFile\N19832.cmc
Initialed by: MDP
final: 7/31/97

INFORMATION REQUEST (IR)

MEMORANDUM OF CONFERENCE

Date: June 23, 1997

Representing Mylan Pharmaceuticals:
John O'Donnell
Andrea Miller

Representing HFD-520:
David Bostwick
Maureen Dillon-Parker
Robert Whiddon, Ph. D.
James Timper

Subject: NDA 19-832, Sulfamylon Solution, 5%.

The Mylan representatives came in to drop off an amendment to the chemistry section of this NDA. Additional submissions to the application are still pending as follows:

1. Statistical amendment (to be delivered June 24, 1997). This amendment will correct some minor errors in the data disks and provide additional analyses on the Cincinnati study.

2. Clinical amendments. The first of these is to be delivered around July 1, 1997, and will correct tables in the original submission which were in error because of incompatibility between computer software packages. The second amendment will be submitted about August 1 and is to contain the data on the patients in the study who did not receive either double antibiotic solution or Sulfamylon Solution. This information was requested by HFD-520 in order to provide a second control group, which could possibly be used as a historical control.

3. A genotoxicity using mammalian cells is to be submitted for review by Dr. Ellis around July 15.

Thus, it appears that the data package for this NDA will not be complete until about August 1. (The NDA was originally resubmitted on April 1, 1997).

/S/

David C. Bostwick, Clinical Reviewer

cc: NDA 19-832
HFD-520/Bostwick
HFD-520/Dillon-Parker
HFD-520/Roberts
HFD-520/Ellis
HFD-530/Lin
HFD-340
HFD-240

DILLON-PARKER
520

NDA 19-832

Mylan Pharmaceuticals, Inc.
Attention: Peter Bruce Bottini, Ph.D.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Dr. Bottini:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Sulfamylon Solution, 5%.

We also refer to the teleconference between representatives of your firm and FDA on February 26, 1998.

As requested, a copy of our minutes of that teleconference are enclosed.

If you have any questions, please contact Maureen Dillon-Parker, Project Manager, at (301) 827-2120.

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

Enclosed documents:
Minutes (4 pages)

cc:
Original NDA 19-832
HFD-520/Div. Files
HFD-520/Tech/MtgFile/Evans
HFD-520/TLC/Roberts
HFD-520/CR/Bostwick
HFD-725/TLStat/Flyer
HFD-725/TLStat/Lin
HFD-725/Stat/Li
HFD-520/PM/DillonParker

Drafted by: mdp/April 23, 1998/n19832.ltr
final: April 23, 1998

GENERAL CORRESPONDENCE (MINUTES SENT)

TELECONFERENCE MINUTES

Meeting Date: February 26, 1998

Time: 1:30-2:30 p.m.

NDA # & Drug Name: NDA 19-832, Sulfamylon 5% Solution

External Participant: Mylan Pharmaceuticals

Type of Meeting: To discuss the Clinical Confirmatory Trial Protocol

Meeting Chair: Maureen Dillon-Parker, Project Manager

External Participant Lead: Peter B. Bottini
Director, Regulatory Affairs Associate

Meeting Recorder: Maureen Dillon-Parker
Project Manager

FDA Attendees:

Gary Chikami, M.D., Division Director
Rosemary Roberts, M.D., Team Leader, Clinical
David Bostwick, Clinical Reviewer
Daphne Lin, Ph.D., Team Leader, Statistics
Yulan Li, Ph.D., Statistical Reviewer
Paul Flyer, Ph.D., Team Leader (HFD-530) Statistics
Maureen Dillon-Parker, Project Manager

External Attendees:

Peter B. Bottini, Pharm.D., Director
John O'Donnell, M.D., Research and Development
Tom Clark, M.D., Medical Director
Andrea Miller, Manager, Regulatory Affairs
Pat McGrath, Ph.D., Assoc. Director, Clinical Research
Bill Richardson, President/CEO, Dow Hickam

A. Meeting Objectives:

- To discuss the Clinical Confirmatory Trial draft protocol dated 17 January 1998.

B. Discussion Points:

- A facsimile was sent on February 25, 1998, requesting that a labeling change be made to the section of the package insert. The current insert reads

The Sponsor proposed revising this statement to read as follows:

COMMENTS ON THE PROTOCOL:

- The sponsor will explore the issue of blinding. The Division recommends blinding because of the different standards-of-care (SOC) and inability to use a placebo. The sponsor stated that this may be difficult because the double-antibiotic may be the only clear antibiotic, the rest are slurry's, gauzes, chlorhexidines, etc.

- If treatment cannot be blinded, the evaluation of the outcomes should be blinded. All treatment failures must be well documented.

- The Sponsor intends to classify infectious graft loss at any time point as a failure.

- Regarding the concomitant medications, the Division would like as much information as possible for evaluation (i.e., start/stop dates, dosages, etc).

- Sponsor stated that graft survival rates are high in most hospitals, therefore, they are concerned with designing an equivalence trial which owuld require a large sample size.

- The sponsor must provide evidence (documentation) that the standard-of-care is active.

- The sponsor stated that there is no literature on the use of gauze with petrolatum as an active control and its effectiveness on preventing graft loss.

- The Division stated that if the sponsor develops an equivalence trial, information on the the activity of the SOC must be submitted. The sponsor stated that the literature contains information on the reduction of microbes, but not on graft loss.

- The Division questioned the role of an interim analysis in that study.

- The Sponsor should consider stratifing the randomization by burn size (20-40% and 40-60%).

- If equivalence is demonstrated then the label will be adjusted to reflect this.

- If clinical benefit is not demonstrated, other benefits to the patient will be considered; however, under the Subpart H regulations, if no benefit is established for sulfamylon solution 5% in this patient population, then the product could be removed from the market.

C. Decisions (agreements) reached/Information to be submitted:

- The sponsor will explore the issue of blinding.
- Revision to the section is acceptable, but may be revised in the future.
- The concomitant medications should be carefully documented by the investigators.
- The sponsor must provide evidence (documentation) that the standard-of-care is active.
- If the sponsor develops an equivalence trial, information on the the activity of the SOC must be submitted.
- The statistical analysis plan should be provided for review.
- The Sponsor should revise the protocol and submit another draft for review.

D. Unresolved issues or issues requiring further discussion:

Division will review the revised protocol when submitted and schedule a teleconference to discuss.

Action Items:

Item	**Responsible Person**	**Due Date**
Submit revised protocol	Mylan	As available

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

cc: NDA 19-832
Division File
HFD-520/DivDir/Chikami/rd 4/25/98
HFD-520/TLClin/Roberts/rd 4/23/98
HFD-520/MO/Bostwick/rd 4/21/98
HFD-725/TLStat/Lin/rd 4/17/98
HFD-725/Stat/Li
HFD-530/TLStat/Flyer/rd 4/17/98
HFD-520/PMS/Dillonparker/tc\N19832.tc
rd/mdp/April 14, 1998
ft/mdp/April 27, 1998

TELECONFERENCE MINUTES

Meeting Date: November 18, 1997

Time: 10:00-10:30 a.m.

NDA # & Drug Name: NDA 19-832, Sulfamylon 5% Solution

External Participant: Mylan Pharmaceuticals

Type of Meeting: To discuss the Labeling and approvability under Subpart H.

Meeting Chair: Maureen Dillon-Parker, Project Manager

External Participant Lead: Peter B. Bottini
Director, Regulatory Affairs Associate

Meeting Recorder: Maureen Dillon-Parker
Project Manager

FDA Attendees:

David Bostwick, Clinical Reviewer
Maureen Dillon-Parker, Project Manager

External Attendees:

Peter B. Bottini, Pharm.D., Director
John O'Donnell, M.D., Research and Development
Frank Sisto, Regulatory Affairs
Andrea Miller, Manager, Regulatory Affairs
Pat McGrath, Ph.D., Assoc. Director, Clinical Research

A. Teleconference Objectives:

- To discuss the Sulfamylon Labeling and the issues for approvability (Subpart H)

B. Discussion Points:

- Discussed the difficulty in publicizing control medications from the Adverse reactions section that are not approved.
- The labeling will have to be reviewed by the Division of Drug Marketing and Advertising (DDMAC).

- Discussed the numbers of patients that had convulsions and inhalation injury together. Mylan stated that 3 patients had pulmonary injury on admission. They will check and see if the patients had underlying seizures prior to injury.

- Mylan will complete the double antibiotic (DAB) column of the labeling.

- Mylan stated that most of the 12 patients with respiratory insufficiency had inhalation injuries also.

- FDA stated that the drug may be approved under the Subpart H - Accelerated Approval regulations [21 CFR 314.500]. This requires them to conduct a clinical confirmatory trial. The purpose of the trial would be to validate the surrogate endpoint.

- Mylan stated that they would work with Dr. McCauley (consultant to Mylan) on a proposed draft protocol for the clinical confirmatory study and would submit a draft protocol for our review.

- Mylan stated that sponsor/investigator IND holders are no longer activating the IND's as they are waiting for the drug to be approved.

- Mylan informed the Division that the mock-up carton and container labeling is being submitted this week, and that a letter should be received from the Orphan Drug Division reflecting the indication change.

/S/

Signature, minutes preparer: _____

/S/

Concurrence Chair (or designated signatory): _____

cc: NDA 19-832
Division File
HFD-520/TLClin/Roberts
HFD-520/MO/Bostwick/rd
HFD-520/PMS/Dillonparker/tc\N19832.118
rd/mdp/November 30, 1997
ft/mdp/December 5, 1997

MEMORANDUM OF TELPHONE CONVERSATION

NDA 19-832
Date: September 17, 1997

Between: Dr. Glenn Warden
Shriners Institute Burn Center
Cincinnati, Ohio

Dr. John O'Donnell
Dr. Bruce Bottini
Dr. Tom Clark
Mylan Pharmaceuticals
Morgantown, West Virginia

and:

David Bostwick
HFD-520

This telecon concerned the clinical study performed by Dr. Warden in support of Mylan's NDA for Sulfamylon Solution, 5%. I had the following questions for Dr. Warden:

1. Q: How did he choose which patients to begin on Double Antibiotic (DAB) solution as opposed to beginning them on DAB plus Sulfamylon?

   A: In general, Dr. Warden picked smaller, less complicated burns to begin with DAB. He began with DAB plus Sulfamylon when the patient was known or suspected to have *Pseudomonas* colonization, or when the patient was a transfer from another facility.

2. Q: Since some patients who began on DAB later had to switch to DAB plus Sulfamylon, why weren't all patients started on the combined regimen?

   A: Dr. Warden did not start all patients on the combined regimen because he has an investigator IND for Sulfamylon, and each patient entered required more paperwork. Having seen the data in support of the NDA, he stated that he now starts all his patients on the combined regimen.

3. Q: How was the combined regimen arrived at?

   A: Dr. Warden uses DAB for *S. aureus* and Sulfamylon for *Pseudomonas*. He feels both are necessary to give a sufficiently wide spectrum of activity.

/S/

David Bostwick

:Orig NDA
HFD-340
HFD-520
HFD-520/CR/Bostwick
HFD-520/TL/Roberts
~~HFD-520~~/PM/Dillon-Parker

HFD-520/~~Est~~/Chikami
HFD-725/Dr. Li

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-832

CORRESPONDENCE

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OCT 09 1997

ary Chikami, M.D.
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ivision of Anti-Infective Drug Products
TTENTION-DOCUMENT CONTROL ROOM
201 Corporate Boulevard, HFD-530
ockville, MD 20850
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RE: SULFAMYLON® (Mafenide Acetate, USP)
FOR 5% TOPICAL SOLUTION
NDA 19-832
ENVIRONMENTAL ASSESSMENT -
REQUEST FOR CATEGORICAL EXCLUSION

ear Dr. Chikami:
C - Aqua

Pursuant to 21 CFR 25.15(d) and 25.31(b), Mylan Pharmaceuticals Inc. requests categorical exclusion from the requirement to prepare and submit an Environmental ssment for this application. In support of this request, we submit:

1) as provided by 21 CFR 25.31(b) approval of this NDA will result in an increase in the use of the active moiety with an estimated concentration (see Appendix I) of the substance at the point of entry into the aquatic environment which is below one part per billion, and

2) that to the applicants knowledge, no extraordinary circumstances exist.

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ely,

Sisto
Director
Affairs

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599-7284
598-5406

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APPENDIX I

Calculation of Expected Introduction Concentration - Aquatic for NDA 19-832
Sulfamylon® (Mafenide Acetate, USP) for 5% Topical Solution

EIC - Aquatic (ppm) = A x B X C x D[1]

Where A = Kg/year production
B = 1/Liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)

1.115 x 10" Liters per day entering POTW's

5th year production estimates mafenide acetate = 15,000 kg

5th year production estimates mafenide = 11,343 kg

$$15{,}000 \text{ kg} \times \frac{\text{M.W. Mafenide}}{\text{M.W. Mafenide Acetate}} \quad \frac{(186.24)}{(246.29)} = 11{,}343 \text{ kg}$$

$$\text{EIC - Aquatic (ppm)} = 11{,}343 \times \frac{1}{1.115 \times 1011} \times \frac{1}{365} \times 10^6$$

ppm = $27.9 \times 10^{-5} = 0.000279$

ppb = 0.279

[1]Source: Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements (CDER) November 1995; p. 14.

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FEB 25 1998

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ORIG AMENDMENT

ORIGINAL

Gary K. Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION - DOCUMENT CONTROL ROOM
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

LABELING CORRESPONDENCE

RE: NDA 19-832
SULFAMYLON® (Mafenide Acetate, USP) For 5% Topical Solution

Dear Dr. Chikami:

Reference is made to the New Drug Application identified above, that is currently pending final approval. As was previously discussed with the Division, Mylan is proposing a revision in the section of the package insert. Mylan wishes to discuss this revision with the Division during the scheduled February 26, 1998 telephone conference.

The proposed revision in the section of the package outsert is as follows:

Current Insert	Proposed Changes[1]

[1] ~~Strikeouts~~ refer to proposed deletions and underlined shaded text to proposed additions.

This revision is supported by data found in the Fort Sam report, **Retrospective Review of Current and Historical Use of Sulfamylon® (mafenide acetate, USP) 5% Topical Solution in the Treatment of Burned Soldiers: 1968 - 1996**, provided in the March 27, 1997 amendment to the referenced NDA. In the Fort Sam study, dressings were soaked with Sulfamylon® 5% Topical Solution every six to eight hours. A copy of page of the Fort Sam study that describes the method of administration of Sulfamylon® 5% Topical in the management of burn patients receiving skin grafts is attached.

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Sales & Marketing (304) 598-3232

This amendment is provided in duplicate. Should you have any questions or comments regarding this submission, please contact the undersigned by telephone at (304) 599-2595, ext. 6600, or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

enclosures

R:\NDA\SULFAMY\LETTER-022498

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FEB 12 1998

Gary K. Chikami, M.D.
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION-DOCUMENT CONTROL ROOM
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

RE: SULFAMYLON® (Mafenide Acetate, USP)
Powder for 5% Topical Solution
NDA 19-832

Dear Dr. Chikami:

Mylan's March 27, 1997 amendment to the above referenced application lists the dimensions of the packaging system for the Sulfamylon product as being 4" x 6 ½" with a seal area of 1/4" (refer to Vol. 2, p. 3-184). Based on the production experience to date it has been found desirable to make a slightly larger package in order to prevent both excessive stretching of the sealed sides of the pouch and potential powder blow-back during the filling process.

The nominal dimensions of the pouch have therefore been changed to 4⅝" x 7" with a seal area of 3/8". No other changes have been made to the package and no changes in the quality of the product are anticipated as a result of the change in package size. Based on our previous commitment, the first three production lots and at least one lot yearly thereafter will be entered into the long-term stability monitoring program for this product.

Pursuant to 21 CFR 314.60(c), we certify that a true copy of this amendment, as submitted to the Center for Drug Evaluation and Research, Division of Anti-Infective Drug Products, has been forwarded to the FDA's Baltimore District Office.

This amendment is provided in duplicate. Should you have any questions or comments regarding this submission, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

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[RDLIB NDA SULFAMYL]PACKAGING-SIZE-CHANGE_021298.WPD

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FEB 6 1998

ORIGINAL

Gary K. Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION - DOCUMENT CONTROL ROOM
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

LABELING CORRESPONDENCE

RE: NDA 19-832
SULFAMYLON® (Mafenide Acetate, USP) For 5% Topical Solution

Dear Dr. Chikami:

Reference is made to the New Drug Application identified above, that is currently pending final approval, to the Agency's November 26, 1997 "approvable" letter that contained draft labeling and to the Agency's comments pertaining to the labeling that were forwarded to Mylan by facsimile on January 15, 1998. At this time Mylan wishes to amend this application to provide final printed labeling. Enclosed are sixteen copies of each of the following:

- Final Printed Package Insert
- Printer's Proof Packet Labeling
- Printer's Proof Carton Labeling

Of the sixteen copies provided, ten copies are individually mounted on card stock paper and the remaining six copies are provided in the white Tyvex® envelope attached to this submission. The enclosed labeling is identical in content to the draft labeling provided in the Agency's November 26, 1997 letter except for revisions made in accordance to the Agency's comments provided in the January 15, 1998 facsimile.

This amendment is provided in duplicate. Should you have any questions or comments regarding this submission, please contact the undersigned by telephone at (304) 599-2595, ext. 6600, or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

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DUPLICATE

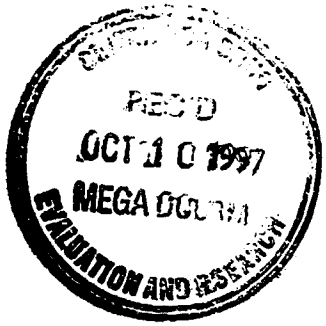
MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 09, 1997

BC

ORIG AMENDMENT



Gary Chikami, M.D.
Acting Division Director
Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products
ATTENTION - DOCUMENT CONTROL ROOM
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

CMC AMENDMENT

RE: NDA 19-832: SULFAMYLON® (Mafenide Acetate, USP) for 5% Topical Solution

Dear Dr. Chikami:

Reference is made to the pending New Drug Application identified above for SULFAMYLON® for 5% Topical Solution, and to Mylan's March 27, 1997, June 23, 1997, and August 29, 1997 amendments to this NDA. The March 27, 1997 amendment contained a revised Chemistry, Manufacturing, and Controls section that included an Environmental Assessment. Mylan's June 23, 1997 amendment was a CMC amendment regarding the process submitted in response to the Agency's comments dated May 07, 1997. Mylan's August 29, 1997 amendment was also a CMC amendment regarding the process submitted in response to the Agency's comments dated July 31, 1997.

The purposes of this submission are as follows:

1. Replace the Environmental Assessment submitted in the March 27, 1997 amendment with a Request for a Categorical Exclusion from the requirement to submit an Environmental Assessment;
2. Update the SULFAMYLON® for 5% Topical Solution stability submitted in Mylan's June 23, 1997 amendment;
3. Revise the storage directions of the prepared solution submitted in the August 29,1997 to note that the solution can be stored at room temperature instead of refrigeration;
4. Provide for as an additional microbiological testing facility.

Environmental Assessment

Mylan's March 27, 1997 amendment provided an abbreviated Environmental Assessment. A purged copy of the Environmental Assessment for FOI release was submitted in the June 23, 1997 amendment. On July 01, 1997, the Division sent a facsimile to Mylan that contained comments on the Environmental Assessment form the EA Review Team. However, the Food and Drug Administration (FDA) amended the regulations regarding the requirements for the submission of an Environmental Assessment after July 01, 1997. The final rule was published in the July 29, 1997 Federal Register (Vol. 62, No. 145). Pursuant to the revised regulations [21 CFR 25.15(d) and 25.31(b)], Mylan is requesting a categorical exclusion from the requirement to prepare and submit an Environmental Assessment for this application. The Request for Categorical Exclusion is provided in Attachment A.

Stability Data

Two (2) months of stability data on three lots of SULFAMYLON® was submitted in the June 23, 1997 amendment. Since that time, additional stability data has been obtained. Attachment B contains three (3) months of stability data on three lots of SULFAMYLON® under accelerated (40° C/75% Relative Humidity) and room temperature (25° C/60% Relative Humidity) conditions. These three (3) lots were at which is an intensity greater than Mylan anticipates using for sterilization. This dosage level was chosen to enhance any possible chemical or physical derogation that may occur due to Even at this level of exposure no deleterious effects are seen on potency, acetic acid content, pH, related compounds or physical characteristics of SULFAMYLON®.

Based on the stability data on SULFAMYLON® submitted in the March 27, 1997 amendment and on the stability data of SULFAMYLON® that demonstrates that does not impact the chemical or physical characteristics of SULFAMYLON®, Mylan is requesting an 18 month expiration date.

Prepared Solution Storage Directions

Mylan's response to FDA Comment 2 contained in the August 29, 1997 noted that the stability data supported SULFAMYLON® 5% Solution for eight days when stored under refrigeration. This response indicated that the labeling would direct that the prepared solution be used in 48 hours of preparation and stored under refrigeration. However, Mylan also submitted data in Volume 2 of the March 27, 1997 amendment on page 3-222 (sterile saline) and on page 3-224 (sterile water) to support that the SULFAMYLON® Solution does not produce bacterial growth after eight days when stored at room temperature (27.5° ± 2.5° C). Therefore, Mylan is changing the label instructions to direct that the SULFAMYLON® 5% Solution be used within 48 hours of preparation and stored at **room temperature, 25° to 30° C.**

Microbiological Testing

Microbiological testing performed for product release, stability, and the periodic audit of the product's sterilization process will be conducted by either Mylan Pharmaceuticals or is a contract analytical facility located at

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical section of this amendment, as submitted to the Division of Anti-Infective Drug Products, has been forwarded to the FDA's Baltimore District Office.

This amendment is provided in duplicate. One (1) desk copy has been sent to Dr. Temper under a separate cover. Any questions or concerns regarding this amendment should be addressed to the attention of the undersigned at telephone number (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director, Regulatory Affairs

enclosures

[RDLIB.IND.SULFAMYLON]100897-amend

MYLAN PHARMACEUTICALS INC

DUPLICATE

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October 08, 1997

Gary Chikami, M.D.
Acting Division Director
Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products
ATTENTION - DOCUMENT CONTROL ROOM
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

LABELING AMENDMENT

RE: NDA 19-832: SULFAMYLON® (Mafenide Acetate, USP) for 5% Topical Solution

Dear Dr. Chikami:

Reference is made to the pending New Drug Application identified above for SULFAMYLON® for 5% Topical Solution and to Mylan's March 27, 1997 amendment to this NDA. The March 27, 1997 amendment contained draft labeling for the packet, carton and outsert for SULFAMYLON® POWDER for 5% Topical Solution.

The purpose of this submission is to revise the draft labeling submitted in the March 27, 1997 amendment. Four (4) draft copies of the revised packet, carton and outsert are provided in Attachment C. The labeling for the packet and carton was revised as follows:

1. Deleted the word from the official name of the product
2. Indicated that the powder is sterile
3. Modified the storage statement to match the storage statement in the prescribing information

The outsert was revised as follows:

1. Combined information for SULFAMYLON® Cream with information for SULFAMYLON® for 5% Topical Solution to provide a common outsert for both products.
2. Expanded the CLINICAL PHARMACOLOGY and ADVERSE REACTIONS sections to include additional data for SULFAMYLON® POWDER for 5% Topical Solution.

The sources of information for the revised outsert are the referenced NDA, amendments to the referenced NDA and outserts approved for SULFAMYLON® Cream. The annotated outsert provided in Attachment A references each information source. Annotations to the NDA and supplements to the NDA are referenced by the date of the submission of the NDA/supplement followed by the volume number and page number(s) where the information can be located. For example an annotation of 03/27/97;2:3-1 to 3-5 references information found on pages 3-1 to 3-5 in Volume 2 of the March 27, 1997 amendment. Annotations to SULFAMYLON® Cream outserts include the date that the outsert was approved by the Agency. For the convenience of the reviewer, the current SULFAMYLON® Cream outsert approved on November 01, 1988 is provided in Attachment B. The original SULFAMYLON® Cream outsert approved on January 24, 1969 is provided in Attachment C.

This amendment is provided in duplicate. One (1) desk copy has been sent to Dr. David Bostwick under a separate cover. Any questions or concerns regarding this amendment should be addressed to the attention of the undersigned at telephone number (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto

Frank R. Sisto
Executive Director, Regulatory Affairs

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ORIGINAL

MYLAN PHARMACEUTICALS INC

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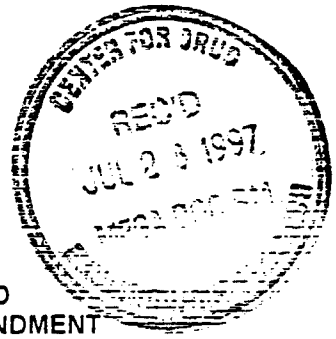
July 25, 1997



David W. Feigal, Jr., M.D.
Acting Director
Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products
Document Control Room
9201 Corporate Boulevard
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Rockville, MD 20850

CLINICAL/STATISTICAL AND PHARMACOKINETICS AMENDMENT

RE: NDA 19-832: SULFAMYLON® (Mafenide Acetate, USP)
POWDER for 5% Topical Solution

Dear Dr. Feigal:

Reference is made to the pending New Drug Application identified above for SULFAMYLON® Powder for 5% Topical Solution and to Mylan's March 27, 1997 amendment to this NDA. The purpose of this submission is to provide pharmacokinetic data on topical mafenide acetate and data from the 149 patients who were excluded from the data analyses submitted March 27, 1997.

Mylan reviewed the literature for information regarding the pharmacokinetics of SULFAMYLON®. Three references were found that report the pharmacokinetics of mafenide acetate following topical application. The three articles along with a summary of the available information is provided in Part I of this amendment and constitutes the pharmacokinetics section of this application.

As requested by the Agency, data for the 149 patients from the Cincinnati Study site who were not previously submitted to the NDA is provided in Part II of this amendment. These patients were excluded from the analyses submitted in the March 31, 1997 amendment because they did not receive DAB alone or DAB/SS5% alone as initial autograft therapy and could not be used to determine the incremental benefit of SS5%. Part II of this amendment contains a summary of the data from these patients along with their case report forms.

During the data resolution process of these 149 patients, it was discovered that two (2) patients had been inappropriately classified as receiving initial treatment other than DAB alone or DAB/SS5% alone. The initial treatment for both of these patients was DAB which qualified them for entry into the group of 438 patients subjected to analysis. Therefore the key efficacy parameter of graft loss was re-analyzed with these two patients included. This re-analysis is provided in Part II of this amendment. Although the addition of these two patients slightly improved the performance of the DAB control group, the original conclusion that cases treated with SS5% received an incremental benefit was not changed. Since the inclusion of these two cases did not change the original conclusions, data for these two patients are presented in Part II with the data for the 147 patients who did not receive DAB alone or DAB/SS5% alone.

This amendment is provided in duplicate. Any questions or concerns regarding this amendment should be addressed to the attention of the undersigned at telephone number (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director, Regulatory Affairs

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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 27, 1997

David W. Feigal, Jr., M.D.
Acting Director
Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products
Document Control Room
9201 Corporate Boulevard
HFD-530
Rockville, MD 20850

CLINICAL/STATISTICAL AND TOXICOLOGY AMENDMENT

RE: NDA 19-832: SULFAMYLON® (Mafenide Acetate, USP)
POWDER for 5% Topical Solution

Dear Dr. Feigal:

Reference is made to the pending New Drug Application identified above for SULFAMYLON® and to Mylan's March 27, 1997 amendment to the NDA. The purpose of this submission is to provide replacement/additional pages to the March amendment and to provide the mutagenicity test report.

During a continued review of the March 27, 1997 amendment, Mylan identified errors and omissions in the submission. PART I of this submission contains replacement and insertion pages that correct the noted errors and omissions. The changes were minor textual and data changes. None of the changes were determined to be major. The corrections described in this submission do not change any conclusion regarding the safety or efficacy assessment of SULFAMYLON®.

Mylan has conducted a mutagenicity test to evaluate the ability of SULFAMYLON® to induce forward mutations at the thymidine kinase locus in the mouse lymphoma L5178Y cell line. The study, "Mutagenicity Test on Sulfamylon Acetate in the L5178Y TK +/- Mouse Lymphoma Forward Mutation Assay" Study No. 18468-0-431) , was completed on June 25, 1997. A copy of the final report for this study is provided in PART II of this submission. In addition, PART II contains a copy of the protocol, that was used in the conduct of the study. The study demonstrated that SULFAMYLON® was considered negative with and without activation at the TK locus in L5178Y mouse lymphoma cells under the conditions used in this study.

PART III of this submission contains descriptions of statistical variables as requested in the Division's June 20, 1997, facsimile. A copy of this facsimile is also provided in PART III.

This amendment is provided in duplicate. Three (3) desk copies have been provided under separate cover. Any questions or concerns regarding this amendment should be addressed to the attention of the undersigned at telephone number (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director, Regulatory Affairs

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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 24, 1997

David W. Feigal, Jr., M.D.
Acting Director
Center for Drug Evaluation & Research
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Document Control Room
9201 Corporate Boulevard
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CLINICAL/STATISTICAL AMENDMENT

RE: SULFAMYLON® (Mafenide Acetate, USP) POWDER for
5% Topical Solution
NDA 19-832
NEW INFORMATION

Dear Dr. Feigal:

Reference is made to the pending New Drug Application identified above for SULFAMYLON® and to Mylan's March 27, 1997 amendment to the NDA. The purpose of this submission is to amend the March 27, 1997 amendment with new statistical analyses and with replacement data disks.

The new statistical analyses provided in this submission are as follows:

1. Section I provides an additional analyses of the bootstrap method done to calculate odds ratios and their corresponding 95%, 90% and 80% confidence intervals for three endpoints: All Cause Graft Loss, Infectious Graft Loss, and Treatment Failure.

2. Section II contains an addendum to the study report on the Cincinnati experience with 5% Sulfamylon solution. The addendum report deals with the Kaplan-Meier and Cox Proportional Hazards Regression analysis of the efficacy endpoints reported in the original submission.

The data disk for the Cincinnati Study has been revised to correct data in file 'eval_ae.ssd01'. Two adverse events for Patient (seizures and hearing loss) had the variable REL (relationship to test material) inadvertently set to 3 and 2, respectively. This variable should have been equal to 1 for both events. The revised disk now contains the correct information. The paper copy of the data listings provided in the March 27, 1997 amendment was correct. An additional data disk for the Cincinnati Study that provides the file 'gr_clm' found in 'boot_strap_5day.sas' has also been provided. This data listing was provided in the paper copy of the data listings in the March 27, 1997 amendment but was not provided on the data disks that accompanied that submission.

The data disk for the Ft. Sam Houston Safety Study has been revised to provide a dataset for information collected on miscellaneous complications. This information was not presented in the paper copy of the data listings nor on the data disks provided in the March 27, 1997 amendment. The data disk provided in this submission has been corrected. In addition a paper copy of this data listing is provided in Section III.

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This amendment is provided in duplicate. Three (3) desk copies have been provided under separate cover. Any questions or concerns regarding this amendment should be addressed to the attention of the undersigned at telephone number (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

DESK COPY

June 24, 1997

Maureen Dillon-Parker,
Project Manager
Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products
Attn: Maureen Dillon-Parker
9201 Corporate Boulevard
HFD-520, Room S306
Rockville, MD 20850

CLINICAL/STATISTICAL AMENDMENT

RE: SULFAMYLON® (Mafenide Acetate, USP) POWDER for
5% Topical Solution
NDA 19-832
NEW INFORMATION

Dear Ms. Dillon-Parker:

Enclosed please find three (3) desk copies of Mylan's amendment of this date providing additional clinical and statistical information. Two of the desk copies and the archival copy contain copies of the referenced replacement data disks

This amendment is also being submitted in duplicate to NDA 19-832. Should you have any questions or require additional clarification about any aspect of this briefing package, please contact the undersigned by phone at (304) 599-2595, ext. 6600 or by telefax at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/enclosures

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN PHARMACEUTICALS INC
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APR 10 1997

Maureen Dillon-Parker, Project Manager
Center for Drug Evaluation and Research
Division of Anti-infective Drug Products
ATTENTION-DOCUMENT CONTROL ROOM
9201 Corporate Boulevard, HFD-520
Rockville, MD 20850

RE: SULFAMYLON® (MAFENIDE ACETATE, USP)
POWDER FOR 5% TOPICAL SOLUTION
NDA 19-832

Dear Ms. Parker:

Enclosed, as requested, is a desk copy of Volumes 1, 2 and 4 through 11 of the March 27, 1997 amendment to our Sulfamylon NDA.

Should you have any questions or require additional information please contact the undersigned by phone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

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Department—Fax Numbers					
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 27, 1997

David W. Feigal, Jr., M.D.
Acting Director
Center for Drug Evaluation & Research
Division of Anti Viral Drug Products
Document Control Room
9201 Corporate Boulevard
HFD-530
Rockville, MD 20850

RE: SULFAMYLON® (Mafenide Acetate, USP) POWDER for
5% Topical Solution
NDA 19-832

Dear Dr. Feigal:

Ownership of the above referenced application has been transferred to Mylan Pharmaceuticals Inc. from Dow Hickam Pharmaceuticals Inc. As the new owner, Mylan:

1) commits to the agreements, promises and conditions made by the former owner and contained in the application,

2) certifies that we have a complete copy of the pending application and

3) commits to advise the FDA about any change in the pending application.

Sincerely,

John O'Donnell

John P. O'Donnell, Ph.D.
Executive Vice President
Research & Quality Control

/maa

Fax Numbers

	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

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March 27, 1997

David W. Feigal, Jr., M.D.
Acting Director
Center for Drug Evaluation & Research
Division of Anti Viral Drug Products
Document Control Room
9201 Corporate Boulevard
HFD-530
Rockville, MD 20850

RE: SULFAMYLON® (Mafenide Acetate, USP) POWDER for
5% Topical Solution
NDA 19-832

Dear Dr. Feigal:

Ownership of the above referenced application has been transferred to Mylan Pharmaceuticals Inc. from Dow Hickam Pharmaceuticals Inc. who previously purchased the application from Sterling Winthrop. Please refer to Attachment 1. Also enclosed (Attachment 2) are Mylan's commitment to complete a study and a copy of the field certification letter (Attachment 3). This amendment addresses one new non-clinical pharmacology study, two new clinical study reports, a revised CMC section and revised proposed draft labeling. An amendment overview is also provided.

Enclosed are data diskettes for protocol 91-02-20-4 (Cincinnati) and the retrospective safety data (U. S. Army Institute of Surgical Research). Each study has two diskettes provided. One disk is in PC SAS format and one is in SAS transport format. All of the diskettes are self extracting zip files.

In addition, there are 68 volumes in the archival copy accompanied by appropriate review copies.

If you should have any questions, please do not hesitate to contact us at (304) 599-2595 extension 6743.

Sincerely,

John O'Donnell

John P. O'Donnell, Ph.D.
Executive Vice President
Research & Quality Control

ATTACHMENT 1
ATTACHMENT 2
ATTACHMENT 3

DUPLICATE

nt—Fax Numbers

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ources	(304) 598-5406

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DOW HICKAM PHARMACEUTICALS

March 25, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD-520
5600 Fishers Lane
Rockville, MD 20857

Attention: Document Control Room 12B-30

RE: NDA 19-832

Reference is made to our pending New Drug Application for Mafenide Acetate 5% (Sulfamylon) Solution, NDA 19-832.

Please be advised that all rights to the application have been transferred to our parent company, Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. This confirms that Mylan Pharmaceuticals Inc. assumes responsibility for all obligations regarding this pending NDA as defined in Section 314 of Title 21 of the Code of Federal Register.

Please address all inquiries to:

Frank Sisto
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, West Virginia 26505
Phone: 304-599-2592

Sincerely,

Barbara Thomas Smith
Director, Regulatory Affairs and Quality Management