

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-743

STATISTICAL REVIEW(S)

CLINICAL/STATISTICAL REVIEW AND EVALUATION

NDA/DRUG CLASS	20-743/ 3S	JUL 11 1997
NAME OF DRUG:	Noritate (Metronidazole 1% cream)	
APPLICANT:	Dermik Labs., Incorporated	
INDICATION(S):	Treatment of Topical Rosacea including Inflammatory Papules, Pustules, and Erythema	
TYPE OF REVIEW:	Clinical/Statistical	
DOCUMENTS REVIEWED:	Study# DL-6027-9510 and Study# DL-6027-9516, Dated September 30, 1996	
CLINICAL INPUT:	Hon-Sum Ko, MD (HFD 540)	

I. INTRODUCTION

Rosacea is a chronic, dermatological disease of unknown etiology. It is characterized by recurrent episodes of inflammatory papules and pustules, usually on the central part of the face, and facial erythema that commonly results in telangiectases. Some patients develop cystic nodules, granulomas, and tissue hypertrophy sometimes leading to rhinophyma in severe cases. Systemically administered metronidazole, an antibacterial/antiprotozoal agent in the nitroimidazole class of compounds, has been among the medications used in the treatment of rosacea.

The sponsor intends to demonstrate the efficacy and safety of once daily application of Noritate 1% cream in a ten week time frame for the indication of topical treatment of rosacea including inflammatory papules, pustules, and erythema.

II. REVIEW

The sponsor has submitted the results of two adequate and well-controlled studies conducted in the U.S. (Studies DL-6027-9510 and DL-6027-9516). In addition to these U.S. clinical trials, two well-controlled studies were conducted in Canada (Studies CMT 1489 and CMT 1286) and 16 supportive studies from the published literature are presented.

Table I summarizes the two U.S. trials, which are the focus of this review.

**Table I
Summary of Studies**

Study #/ (# of Centers)	Study Design, Duration	Treatment Arm (n)	N	Endpoint
DL-6027-9510/ (13)	D.B. Parallel, Randomized, placebo (vehicle) controlled, 10 weeks	Noritate qd (97) Noritate bid (98) Vehicle qd (50) Vehicle bid (48)	293	1) % change: papules, pustules & combined 2) % change: erythema 3) Physician's global evaluation
DL-6027-9516/ (5)	D.B. Parallel, Randomized, placebo (vehicle) controlled, 10 weeks	Noritate qd (104) Vehicle qd (52)	156	1) % change: papules, pustules & combined 2) % change: erythema 3) Physician's global evaluation

The primary endpoint parameters under the review are:

- 1) **Mean Percent Change** from baseline in the **Number of Papules and Pustules**.
At baseline and each visit the number of papules and pustules on the face was counted by the investigator. The number of papules and pustules at the end of treatment were subtracted from the baseline value and then divided by the baseline value to achieve the percent change from baseline.
- 2) **Mean Percentage Change** from baseline in the current **Severity Score for Erythema**. At baseline and each visit the signs/symptoms of erythema were scored based on the severity. The erythema was scored in a scale of 0 to 3, 0 being none, and 3 being severe. The erythema score at the end of treatment was subtracted from the baseline value and then divided by the baseline value to achieve the percent change from baseline.
- 3) **Physician's Global Evaluation Score**. The physicians had assessed the overall severity of rosacea on each patient at the end of treatment. The physicians' global evaluation score was defined from -4 to 6, -4 being worse and 6 being clear.

Although the two primary endpoint variables are "mean percent change in total lesions and erythema score", "mean change in total lesions" at each study visit has been looked at to identify the trend in healing and cure. The conclusions of this review are based only on the mean percent changes as well as the physician's global evaluation score and not on the mean changes.

In order to gain approval for this NDA, the sponsor should demonstrate:

- 1) **Statistical superiority** of Noritate 1% cream to a) Vehicle once-daily and b) Vehicle twice-daily, and

2) **No statistical difference** of Noritate 1% cream once-daily to Noritate 1% cream twice-daily,

at a two-sided, 5% significance level for the percent change in:

1) **Papules and pustules combined** from baseline

2) **Erythema** from baseline, and

3) **Global assessment of the investigator**

For our review purposes, analysis of variance test was performed for all the primary endpoint variables for comparison among the treatment arms, with treatment, investigator, and treatment-by-investigator interactions terms in the model. Pairwise treatment comparisons were made using contrast method as well as Fisher's least square means.

In this review, two different approaches were made. First, the analyses were performed on the data set based on all subjects whose end of treatment values were available and were within a four day window of the 70th day. In other words, subjects whose end of treatment evaluation was before 66 days or after 74 days were eliminated from our evaluable population analyses. This data set will be referred to as FDA-Evaluable (FDA-Eval) data.

Second, in order to maintain the integrity of the randomization, an intent-to-treat analysis was done, based on all randomized subjects whether or not they applied the cream. For the subject with missing 10th week data, the baseline value was carried forward.

Study DL-6027-9510.

Objective, Design, Patient Enrollment and Statistical Methods:

The objective of this study was to compare the efficacy and safety of metronidazole cream 1% and the cream vehicle (placebo) when applied once daily (q.d.) and twice daily (b.i.d.) for 10 weeks in the treatment of moderate to severe rosacea. In addition to comparing metronidazole and the vehicle in each regimen, the regimens were also compared to each other.

This U.S. study was designed as a parallel group, randomized, treatment double-blind, placebo-controlled, evaluator regimen-blind, multicenter, four arm trial. Patients were randomized to either once-daily dose of Noritate, twice-daily dose of Noritate, once-daily dose of the vehicle or twice-daily dose of the vehicle. Patients did not know if they were receiving vehicle or the active treatment, but they were aware of the regimen (q.d. or b.i.d.); the person conducting the efficacy and safety evaluations did not know which treatment the patient was receiving (active or vehicle) and was also unaware of the treatment regimen. Patients were evaluated after 2, 4, 7, and 10 weeks of treatment.

This clinical trial was the first direct comparison of the 1% cream formulation applied once and twice daily.

Based on a two-sided t-test at 0.05 level of significance, and a difference between treatment groups of a 30% change from baseline in erythema with 80% power, a sample size of 228

evaluable subjects was planned in the protocol. However, a total of 293 subjects were enrolled in this study; approximately 29% more patients than originally was intended.

Evaluable Subjects and Dropouts:

The sponsor defined their intent-to-treat population as patients who took at least one dose of medication and had at least one follow-up visit with some efficacy data available and their evaluable population included patients who had completed at least 7 weeks in the study, and had completed a final visit. However, FDA's intent-to-treat and evaluable population were based on the criteria which was mentioned previously in this review.

A total of 49 subjects were not evaluable for this study. The tenth week visit for these subjects was not included in the four day window. (Their visit 10 was either before day 66 or after day 74). Of 293 subjects who enrolled in the study, 244 were found evaluable for our analysis. Five centers had over 20% non-evaluable patients. Table I lists the number and percent of non-evaluable subjects in centers with over 20% non-evaluable subjects.

**Table I
Centers with Higher than 20% Non-Evaluable Subjects**

Evaluable	Center #				
	1	4	5	10	13
	n=21	n=23	n=24	n=24	n=11
Yes	14 (67%)	17 (74%)	17 (71%)	19 (79%)	4 (36%)
No	7 (33%)	6 (26%)	7 (29%)	5 (21%)	7 (64%)

There was no statistically significant difference among the treatment groups in regards to the number of the non-evaluable subjects (p=0.9).

Baseline Comparability:

In the protocol, the sponsor had claimed that 14 investigators will be participating in this study. But, only 13 centers actually took part in the study.

Rosacea is more prevalent in whites, females and adults between the ages of 30 to 55. For these reasons, the majority of subjects (288, 98%) were white, approximately, 2/3 of the subjects were female (190, 65%) and a total of 192 subjects (66%) were between 30 to 55 years old. Thirty percent were older than 55 (88 subjects) and only 4% (11 subjects) were younger than thirty years of age.

The demographic and baseline information of the patients are summarized in Tables II and III.

Table II
Demographics of All Randomized Subjects

	Whole Population (N=293)	Noritate qd (n=97, 33%)	Noritate bid (n=98, 33%)	Vehicle qd (n=50, 17%)	Vehicle bid (n=48, 16%)	P-Value
Age (Mean):	50	49	51	49	50	0.7
Gender (n):						0.04
Male	103 (35%)	34 (35%)	44 (45%)	13 (26%)	12 (25%)	
Female	190 (65%)	63 (65%)	54 (55%)	37 (74%)	36 (75%)	
Investigator (n):						1.00
Eisen	21 (7%)	7 (7%)	7 (7%)	4 (8%)	3 (6%)	
Jacobson	25 (9%)	9 (9%)	8 (8%)	4 (8%)	4 (8%)	
Jorizzo	25 (9%)	8 (8%)	8 (8%)	5 (10%)	4 (8%)	
Kang	23 (8%)	8 (8%)	8 (8%)	3 (6%)	4 (8%)	
Katz	24 (8%)	8 (8%)	8 (8%)	4 (8%)	4 (8%)	
Lebwohl	30 (10%)	10 (10%)	10 (10%)	5 (10%)	5 (10%)	
Medansky	24 (8%)	8 (8%)	8 (8%)	4 (8%)	4 (8%)	
Monroe	30 (10%)	10 (10%)	10 (10%)	5 (10%)	5 (10%)	
Pariser	11 (4%)	3 (3%)	4 (4%)	2 (4%)	2 (4%)	
vin	24 (8%)	8 (8%)	8 (8%)	4 (8%)	4 (8%)	
jiss	15 (5%)	4 (4%)	5 (5%)	3 (6%)	3 (6%)	
Stough	30 (10%)	10 (10%)	10 (10%)	5 (10%)	5 (10%)	
Asarch	11 (4%)	4 (4%)	4 (4%)	2 (4%)	1 (2%)	

The four treatment groups were comparable relative to age but, a statistically significant difference was observed when treatment arms were compared relative to gender ($p=0.04$).

Table III
Baseline Characteristics of All Randomized Subjects

	Whole Population (N=293)	Noritate qd (n=97, 33%)	Noritate bid (n=98, 33%)	Vehicle qd (n=50, 17%)	Vehicle bid (n=48, 16%)	P-Value
Total Papules & Pustules (Mean)	18	19	19	17	17	0.4
Erythema						0.9
Moderate	179 (61%)	56 (58%)	60 (61%)	33 (66%)	30 (63%)	
Moderate to Severe	91 (31%)	32 (33%)	29 (30%)	14 (28%)	16 (33%)	
Severe	23 (8%)	9 (9%)	9 (9%)	3 (6%)	2 (4%)	
Overall Score*						0.2
Moderate	193 (66%)	60 (62%)	67 (68%)	33 (66%)	33 (69%)	
Moderate to Severe	86 (29%)	34 (35%)	22 (22%)	16 (32%)	14 (29%)	
Severe	14 (5%)	3 (3%)	9 (9%)	1 (2%)	1 (2%)	

* The physician's overall assessment of severity of rosacea at baseline

The four treatment groups were comparable with regard to baseline characteristics (p>0.05).

The elimination of the 49 non-evaluable subjects did not change the distribution of demographics and baseline characteristics for the evaluable population.

Efficacy Analysis:

A total of two hundred and forty-four subjects were evaluable for the analysis. Table IV summarizes the mean and mean change in total papules and pustules in the FDA_Eval subjects at every visit.

Table IV
Comparison of Mean Change in Total Papules & Pustules
FDA_Eval Subjects
(Mean±S.D.)

	Noritrate qd (n=82)	Noritrate bid (n=82)	Vehicle qd (n=42)	Vehicle bid (n=38)	P-Value
Week 1	19 ±11	19±11	17±12	17±9	0.45
Week 2	14±11	15±10	14±11	14±10	0.99
Week 4	11±9	11±11	13±10	11±9	0.74
Week 7	10±10	10±10	12±10	11±12	0.57
Week 10	8±8	8±8	11±9	10±9	0.21
Week2-Week1	-5±7	-5±7	-3±6	-3±4	0.2
Week4-Week2	-3±7	-3±9	-1±6	-3±5	0.4
Week7-Week4	-1±6	-2±5	-1±8	0±8	0.6
Week10-Week7	-2±5	-2±4	-1±5	-2±6	0.8
κ10-Week1	-11±9	-12±11	-6±8	-7±8	0.004

As it is shown in Table IV, a statistical significance was observed relative to mean change in total papules and pustules from baseline at the end of 10th week for FDA Evaluable subjects (p=0.004). Pairwise comparison among the four treatments revealed a statistical significance between Noritate once a day and vehicle once a day (p=0.01) and also a statistical significance between Noritate once daily and vehicle twice daily (p=0.03). The contrast method was used for these pairwise comparisons.

Table V
Comparison of Mean Change in Erythema
FDA_Eval Subjects
(Mean±S.D.)

	Noritrate qd (n=82)	Noritrate bid (n=82)	Vehicle qd (n=42)	Vehicle bid (n=38)	P-Value
Week 1	2±0.3	2±0.23	2±0.3	2±0.3	0.34
Week 10	1±0.7	1±0.7	2±0.7	2±0.7	0.04
Week10-Week1	-.88±0.7	-0.8±0.7	-0.4±0.6	-0.7±0.7	0.006

As it is shown in Table V, a statistical significance difference was observed relative to mean

change in erythema from baseline at the end of 10th week for FDA Evaluable subjects ($p=0.006$). Pairwise comparison among the four treatments revealed a highly statistical significance between Noritate once daily and vehicle once a day ($p<0.001$). The contrast method was used for these pairwise comparisons.

Table VI
Comparison of Mean Percent Change in Total Papules & Pustules,
Erythema and Investigator's Global Assessment
At the End of Treatment Period
FDA_Eval Subjects
(Mean±S.D.)

	Noritate qd (n=82)	Noritate bid (n=82)	Vehicle qd (n=42)	Vehicle bid (n=38)	P-Value
Total Pap. & Pust.	-60±40	-60±40	-30±40	-40±40	0.001
Erythema	-60±30	-40±30	-20±30	-30±30	0.01
Global	2±2	3±2	1±1	2±2	0.001

As shown in Table VI, a statistical significance difference was observed relative to mean percent change from baseline, in papules and pustules, erythema as well as the investigator's global assessment for FDA Evaluable subjects. Pairwise comparison among the four treatments revealed statistical significance between Noritate once daily and vehicle once a day ($p=0.001$) in all three of the primary endpoints.

However, comparing Noritate once a day to vehicle twice a day did not show a statistical significance for percent change in erythema ($p=0.2$) and only borderline significance was observed for the investigator's global assessment ($p=0.07$). Percent change in the total papules and pustules barely showed a statistical significance when Noritate once daily arm was compared to vehicle twice daily ($p=0.05$). The contrast method was used for these pairwise comparisons.

Table VII
Comparison of Mean Change in total Papules & Pustules
FDA_ITT Population
(Mean±S.D.)

	Noritate qd (n=97)	Noritate bid (n=98)	Vehicle qd (n=50)	Vehicle bid (n=48)	P-Value
Week 1	19±11	19±11	17±11	17±9	0.43
Week 10	8±9	9±10	12±11	12±10	0.04
Week10-Week1	-11±10	-10±12	-5±9	-5±8	0.001

Pairwise comparisons among treatment groups revealed statistical differences between Noritate once daily and vehicle once daily and also between Noritate once daily and vehicle twice daily for mean at week 10 and mean change from baseline at week 10 for total papules and pustules in the FDA_ITT population ($p < 0.05$).

Table VIII
Comparison of Mean Change in Erythema
FDA_ITT Population
(Mean±S.D.)

	Noritate qd (n=97)	Noritate bid (n=98)	Vehicle qd (n=50)	Vehicle bid (n=48)	P-Value
Week 1	2±0.3	2±0.23	2±0.3	2±0.3	0.7
Week 10	1±0.7	2±0.7	2±0.7	2±0.7	0.008
Week10-Week1	-0.84±0.7	-0.7±0.7	-0.4±0.6	-0.5±0.7	0.001

Pairwise comparisons among treatment groups showed statistical differences among Noritate once daily and vehicle once daily and also between Noritate once daily and vehicle twice daily ($p < 0.05$) for mean at week 10 and mean change from baseline at week 10 in erythema score in FDA_ITT population.

Table IX
Comparison of Mean Percent Change in Total Papules & Pustules,
Erythema and Investigator's Global Assessment @ Week 10
FDA_ITT Population
(Mean±S.D.)

	Noritate qd (n=97)	Noritate bid (n=98)	Vehicle qd (n=50)	Vehicle bid (n=48)	P-Value
Total Pap.&Pust.	-60±40	-50±60	-30±40	-30±40	0.001
Erythema	-40±30	-30±30	-20±30	-20±30	0.01
Global	2±2	2±2	1±2	1±2	0.001

Pairwise comparisons among treatment groups in the FDA_ITT population revealed statistical differences between Noritate once daily and vehicle once daily and between Noritate once daily and vehicle twice daily ($p < 0.01$) for mean percent change from baseline at week 10 in all the three primary endpoint variables. No statistical significance was observed when Noritate qd was compared to Noritate bid ($p > 0.05$).

Subset Analysis:

Since sample size per center per treatment is too small, a full model having center as an effect in the model is not appropriate. In order to look at the gender interaction, analyses were

performed with gender effect in the model.

These analyses were done on intent-to-treat and evaluable populations on the three primary endpoint variables, percent change in total papules and pustules, erythema and on global assessment of the investigator.

The subset analysis of gender showed the same statistical significance which was observed in the analysis without the gender effect in the model. Noritate once daily was statistically superior to vehicle once daily and vehicle twice daily in all of the primary endpoint variables ($p < 0.05$), when adjusted for gender.

Safety:

According to the reviewing medical officer the data presented did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

Conclusions:

FDA Eval:

According to the findings of this study, statistical significance difference was observed among the treatment groups relative to mean percent change from baseline in papules and pustules and erythema as well as the investigator's global assessment for FDA Evaluable subjects. Pairwise comparison among the four treatments revealed statistical significance between Noritate once daily and vehicle once a day ($p = 0.001$) in all three of the primary endpoints.

However, comparison of Noritate once a day to vehicle twice a day did not show a statistical significance for percent change in erythema ($p = 0.2$) and only borderline significance was observed for the investigator's global assessment ($p = 0.07$). Percent change in the total papules and pustules barely showed a statistical significance when Noritate once daily arm was compared to vehicle twice daily ($p = 0.05$).

FDA ITT:

Comparisons among treatment groups in the FDA_ITT population revealed statistical differences between Noritate once daily and vehicle once daily and between Noritate once daily and vehicle twice daily ($p < 0.01$) for mean percent change from baseline at week 10 in all the three primary endpoint variables.

No statistical significance was observed when Noritate qd was compared to Noritate bid ($p > 0.05$).

Subgroup analysis by gender revealed no interaction effect for the model in the analysis.

Study DL-6027-9516.

Objective, Design, Patient Enrollment and Statistical Methods:

The objective of this study was to compare the efficacy and safety of metronidazole cream 1% and the cream vehicle (placebo) when applied once daily (q.d.) for 10 weeks in the treatment of moderate to severe rosacea.

This was a U.S. randomized, double-blind, parallel group, vehicle-controlled, multicenter trial. Patients were assigned to one of two treatment groups: metronidazole cream 1% q.d. or vehicle q.d. Patients were evaluated at baseline week 2, week 4, week 7, and week 10. At each visit, the number of papules and pustules on the face was counted, the signs/symptoms of erythema were scored, and the investigator made a global evaluation of the change from baseline.

The sponsor had planned to enroll a total of 114 subjects based on a ratio of 2:1 between active and placebo, using a two-sided t-test at the 0.05 level of significance, and a difference between treatment groups of a 30% change from baseline in erythema with 80% power. However, a total of 156 subjects were enrolled in to the study.

Evaluable Subjects and Dropouts:

A total of 30 (19%) subjects were not evaluable for this study. The tenth week visit for these subjects was not included in the four day window. (Their visit 10 was either before day 66 or after day 74). Of 156 subjects who enrolled in the study, 126 were found evaluable for our analysis. Two centers had over 20% non-evaluable patients. Table X lists the number and percent of non-evaluable subjects in centers with over 20% non-evaluable subjects.

**Table X
Centers with Higher than 20% Non-Evaluable Subjects**

Evaluable	Center #	
	4 (n=34)	5 (n=20)
Yes	22 (65%)	15 (75%)
No	12 (35%)	5 (25%)

There was no statistically significant difference among the treatment groups in regards to the number of non-evaluable subjects (p=0.2).

Baseline Comparability:

A total of 156 subjects were enrolled in this study. Of which 109 (70%) were between 30 to 55 years of age, 39 (25%) were older than 55 and 7 (5%) were younger than 30. Fifty (32%) subjects were male and 106 (68%) female. One hundred and fifty (96%) were white. A total of five centers participated in this trial.

The demographic and baseline information of the patients are summarized in Tables XI and XII.

Table XI
Demographics of All Randomized Subjects

	Whole Population (N=156)	Noritate qd (n=104, 66%)	Vehicle qd (n=52, 34%)	P-Value
Age (Mean):	48	49	47	0.3
Gender (n):				0.3
Male	50 (32%)	36 (35%)	14 (27%)	
Female	106 (68%)	68 (65%)	38 (73%)	
Investigator (n):				0.9
Berneman	36 (23%)	24 (23%)	12 (23%)	
Hevia	30 (19%)	20 (19%)	10 (19%)	
Hino	36 (23%)	24 (23%)	12 (23%)	
Stewart	34 (22%)	22 (21%)	12 (23%)	
Stiller	20 (13%)	14 (13%)	6 (12%)	

Table XII
Baseline Characteristics of All Randomized Subjects

	Whole Population (N=156)	Noritate qd (n=104, 66%)	Vehicle qd (n=52, 34%)	P-Value
Total Papules & Pustules (Mean):	16	15	18	0.04
Erythema				0.2
Moderate	118 (76%)	76 (73%)	42 (81%)	
Moderate to Severe	20 (13%)	17 (16%)	3 (6%)	
Severe	18 (12%)	11 (11%)	7 (13%)	
Overall Score				0.2
Moderate	124 (81%)	83 (81%)	41 (79%)	
Moderate to Severe	22 (14%)	16 (16%)	6 (12%)	
Severe	8 (5%)	3 (3%)	5 (10%)	

As shown in the Table XII, the treatments were not homogeneous relative to the total number of papules and pustules at baseline. There was a statistically significant difference between the two treatments at baseline ($p=0.04$).

The elimination of the 30 non-evaluable subjects did not change the distribution of demographics for the evaluable population ($p>0.05$). However, the mean total papules & pustules was not statistically significant anymore and demonstrated only borderline significance ($p=0.08$).

Efficacy Analysis:

A total of one hundred and twenty-six subjects were evaluable for the analysis. Table XIII summarizes the mean and mean change in total papules and pustules in the FDA_Eval subjects at every visit.

**Table XIII
Comparison of Mean Change in Total Papules & Pustules
FDA_Eval Subjects
(Mean±S.D.)**

	Noritate qd (n=81)	Vehicle qd (n=45)	P-Value
Week 1	15±8	18±12	0.08
Week 2	11±7	16±12	0.001
Week 4	9±6	15±13	0.002
Week 7	8±8	15±14	0.001
Week 10	7±8	15±13	0.001
Week2-Week1	-5±7	-2±8	0.07
Week4-Week2	-1±6	-1±7	1
Week7-Week4	-1±6	0±9	0.2
Week10-Week7	-1±6	0±8	0.8
Week10-Week1	-8±10	-3±10	0.01

As is shown in Table XIII, a statistical significance was observed relative to mean change in total papules and pustules from baseline at the end of 10th week period for FDA_Evaluable subjects in the comparison of Noritate once daily and vehicle once daily (p=0.01).

Table XIV
Comparison of Mean Change in Erythema
FDA_Eval Subjects
(Mean±S.D.)

	Noritate qd (n=81)	Vehicle qd (n=45)	P-Value
Week 1	2±0.3	2±0.4	0.7
Week 10	1±0.7	2±0.8	0.003
Week10-Week1	-0.9±0.7	-0.5±0.6	0.002

Highly statistically significant difference was observed between Noritate and vehicle in terms of mean and mean change in erythema at week 10 for evaluable subjects ($p < 0.01$).

Table XV
Comparison of Mean Percent Change in Total Papules & Pustules,
Erythema and Investigator's Global Assessment
FDA_Eval Subjects
(Mean±S.D.)

	Noritate qd (n=81)	Vehicle qd (n=45)	P-Value
Total Papules & Pustules	-50±60	-20±50	0.002
Erythema	-40±30	-20±30	0.003
Global	3±2	1±2	0.001

Highly statistically significant differences were observed between Noritate and vehicle in terms of mean percent change in total papules and pustules, erythema and the investigator's global assessment at week 10 for evaluable subjects ($p < 0.01$).

Since the baseline total number of papules and pustules were different for the two treatments arms, an analysis of covariance was performed on the 'mean change in total papules & pustules' and also in 'percent change in total papules & pustules' by including the baseline value as a covariate in the model. Similar highly statistically significant results were observed ($p < 0.01$).

The analyses performed on the intent-to-treat population yielded similar statistically significant results.

Subset Analysis:

In order to look at the gender and investigator interactions, analyses were performed with gender and center effects in the model.

These analyses were done on intent-to-treat and evaluable population on the three primary endpoint variables, percent change in total papules and pustules, erythema and on global assessment of the investigator.

The subset analysis of gender and center showed the same statistical significance which was observed in the analysis without the gender or investigator effects in the model. Noritate once daily was statistically superior to vehicle once daily in all of the primary endpoint variables ($p < 0.05$), when adjusted for gender and investigator.

Safety:

According to the reviewing medical officer the data presented did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

Conclusions:

FDA Eval

According to the findings of this study, highly statistically significant differences were observed between Noritate qd and vehicle qd relative to the mean percent change in total papules and pustules, erythema and the investigator's global assessment at week 10 for evaluable subjects ($p < 0.01$).

Since the baseline total number of papules and pustules were different for the two treatment arms, an analysis of covariance was performed on the 'mean change in total papules & pustules' and also in 'percent change in total papules & pustules' by including the baseline value as a covariate in the model. Similar highly statistically significant results were observed ($p < 0.01$).

FDA ITT

The analyses performed on the intent-to-treat population yielded similar statistically significant results.

Noritate once daily is statistically significantly superior to vehicle once daily relative to the mean percent change in total papules and pustules, erythema and the global assessment of the investigator in the intent-to-treat and evaluable populations ($p < .05$).

Subgroup analysis by gender and center revealed no interaction effect for the model in the analysis.

III. CONCLUSIONS (Which may be conveyed to the sponsor):

The results of the studies DL-6027-9510 and DL-6027-9516 provide statistical evidence to the applicant's claim that Noritate (metronidazole 1% cream) once daily is superior to vehicle once daily in treatment of Rosacea in a 10 week period.

According to the reviewing medical officer the data presented did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

Shahla S. Farr 7/11/97

Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics IV

Sh. S. Farr July 11, '97

concur: R. Srinivasan, Ph.D.
Team Leader, Biometrics IV

cc:

Archival-NDA 20-743

HFD-540

HFD-540/Dr. Ko

HFD-540/Dr. Walker

HFD-540/Dr. Wilkin

HFD-540/Ms. Cintron

HFD-725/Ms. Farr

HFD-725/Dr. Srinivasan

HFD-725/Dr. Harkins

HFD-344/Dr. Carreras

Chron.

This review contains 16 pages.

Farr\X7-2037\wpfiles\sri\Noritate\nda20743.rev Dated 2/19/97

NOV 14 1991

Statistical Review and Evaluation

NDA/Serial No: 20-743

Name of Drug: Noritate® (metronidazole) Cream, 1%

Applicant: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426-0107

Type of Review: Stability review.

Documents Reviewed: Letter dated 1 August 1997 describing data set.

Chemist: Dr. Higgins, HFD-540

Introduction:

Current regulations require an expiration dating period to appear on the container label for every marketed drug. The expiration dating period is defined as the time interval that a drug is expected to remain within the approved specifications after manufacture. Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological specifications. Assurances that the product in its container will be suitably stable for an anticipated shelf life must come from an accumulation of data on the packaged drug. These stability data involve selected parameters which, taken together, form the stability profile.

Usually, the degradation curve of a product characteristic can be adequately represented by a linear function of time. If the drug characteristic is expected to decrease (or increase) with time, the shelf life is estimated as the time period at which the lower (upper) 95% confidence bound for the mean degradation curve intersects the lower (upper) specification limit. The confidence bound is obtained by using normal theory ordinary least squares.

Model Selection: Tests for Pooling Stability Data

Since different batches of a drug may have different degradation patterns, at least three batches are required to estimate batch-to-batch variability and to test the hypothesis that a single expiration dating period is justifiable for all batches. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data of the individual batches and testing for equality of slopes and/or intercepts to these per batch models. If the degradation curves are similar, it is preferable to pool the data to get a more accurate estimate of the expiration period. If batch-to-batch variability is small, the data

from individual batches are combined into one overall estimate, which usually results in longer estimated expiration dating periods. One of the following models is selected on the basis of the poolability tests:

Model 1. Common intercept, common slope;

Model 2. Separate intercept, common slope;

Model 3. Common intercept, separate slope;

Model 4. Separate intercept, separate slope.

Under Models 2-4, the final expiration dating period is estimated by the minimum of the estimated expiration periods of the individual batches.

Extrapolation Beyond the Observed Data

In the estimation of an expiration dating period, the observed data are used to fit a regression line and construct 95% confidence bounds around the mean degradation line. The estimate of the expiration dating period is the point of the earliest intersection of the confidence interval with the upper or lower product specification limit. This estimate of an expiration period is simply the forecasting of a time point when the mean drug characteristic is likely to still be within the prescribed range. For example, if the sponsor submitted data for 60 months, the assumption is made that the degradation pattern seen within 60 months will continue throughout the estimated expiry period. This assumption can only be verified by the collection of data over the total range of the requested expiration period and is not satisfied by the fact that the extrapolation provided for a long expiration period.

Computational Methods

Statistical analyses of the assay data for this stability analysis were performed by this reviewer using the "Drug Stability Analysis Programs" created at CDER, FDA, as revised on March 26, 1996. Two programs were used. The first program, STABEST.SAS, analyzes the stability data by fitting simple linear regression to each set of batch data. Then the program runs tests for pooling from several batches. Based on the tests, one of the Models 1-4 above is chosen. The results of the program are presented for each batch in the form of the regression equation and estimated expiration period.

The second program, STABPLOT.SAS, plots the 95% confidence limits for the selected drug characteristics.

Results

The sponsor submitted data for the stability analysis of Noritate (metronidazole) cream, 1%. Only the data for assay were in a usable format. Since for each batch there is only one value at each time point, one might speculate that the data provided by sponsor are actually the means of several measurements at that time point. For other presumably measurable characteristics, only ranges or upper bounds were presented. There were three batches, labeled: 5H099A, 5K072A, and CE54D. The exact conditions under which each batch was held were not apparent from the limited documentation held by this reviewer.

This reviewer analyzed the data from the three batches using the FDA programs STABEST.SAS and STABPLOT.SAS. The results from these programs are included in the following.

The poolability test for the three batches indicated clear differences in intercepts. So each batch was fit with a model having a separate intercept and a common slope across batches.

Figure 1. Poolability Test

Drug Stability Analysis

NDA 20-743
 Drug Name: Noritate (Metronidazole) Cream

Test of Batch Poolability (p-value cutpoint used: 0.25)

BY VARIABLE	SOURCE	SS	DF	MS	F	P
ASSAY	Com Int Com Slo	40.60	4	10.15	3.04	0.0650
	Sep Int Com Slo	40.56	2	20.28	6.07	0.0168
	Sep Int Sep Slo	0.04	2	0.02	0.01	0.9934
	Residual	36.78	11	3.34		

Figure 2. Estimated Expiration Period

Drug Stability Analysis

NDA 20-743

Drug Name: Noritate (Metronidazole) Cream

Estimate of Expiry Period

A (D) indicates that the parameter represents the dissolution activities
 An (A) indicates that the parameter represents the assay values

By Variable	----- Fitted Line -----	BATCH NUMBER	Estimated Expiry Period
ASSAY(A)	$Y=100.5386 + -0.1300 * \text{Time}$	5H099A	34 .
	$Y=102.4719 + -0.1300 * \text{Time}$	5K072A	40
	$Y=98.6122 + -0.1300 * \text{Time}$	CE54D	27
		"MIN. TIME"	27

Note that the minimum estimated expiration date is thus 27 months.

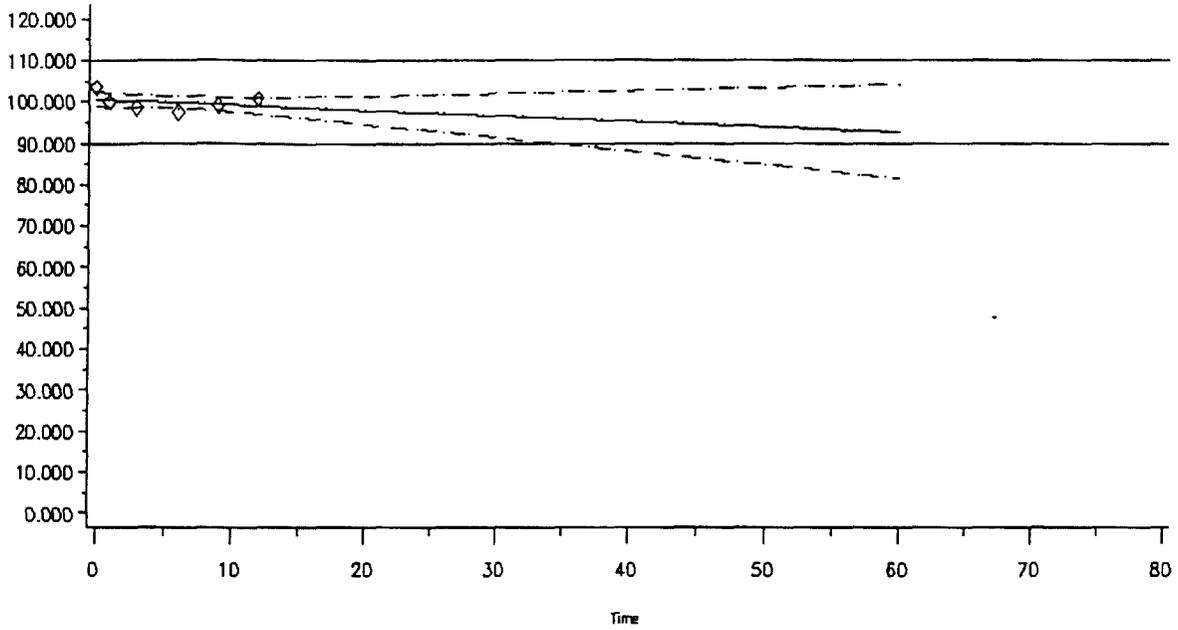
Figure 3. 95% Confidence Interval Plot for Batch 5H099A

Stability Analysis

Variable Selected: ASSAY

Variable Type: Assay

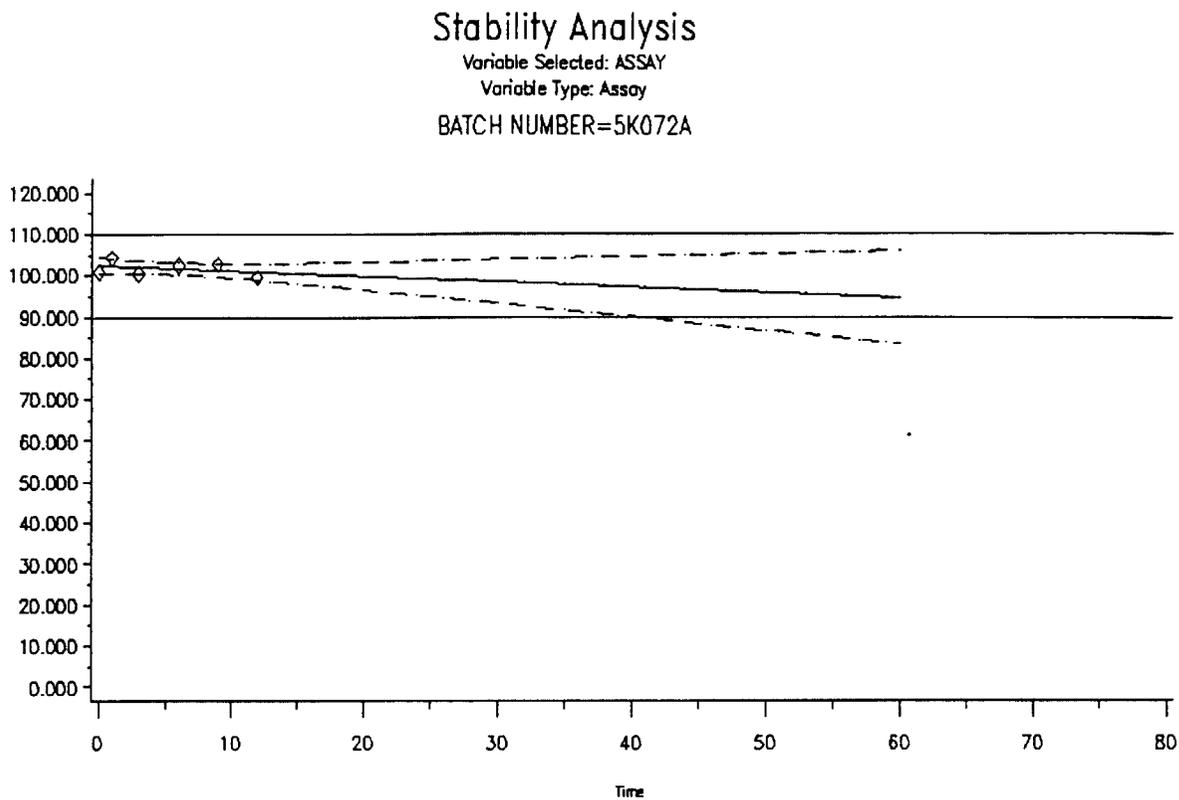
BATCH NUMBER=5H099A



Legend: $\diamond \diamond \diamond$ Observed — Predicted - - - Upper CI - - - Lower CI

Type of Confidence Intervals: 95 % 2-Side CIs of Mean predicted values

Figure 4. 95% Confidence Interval Plot for Batch 5K072A



Legend: ◊ ◊ ◊ Observed — Predicted - - - Upper CI - . - Lower CI

Type of Confidence Intervals: 95 % 2-Side CIs of Mean predicted values

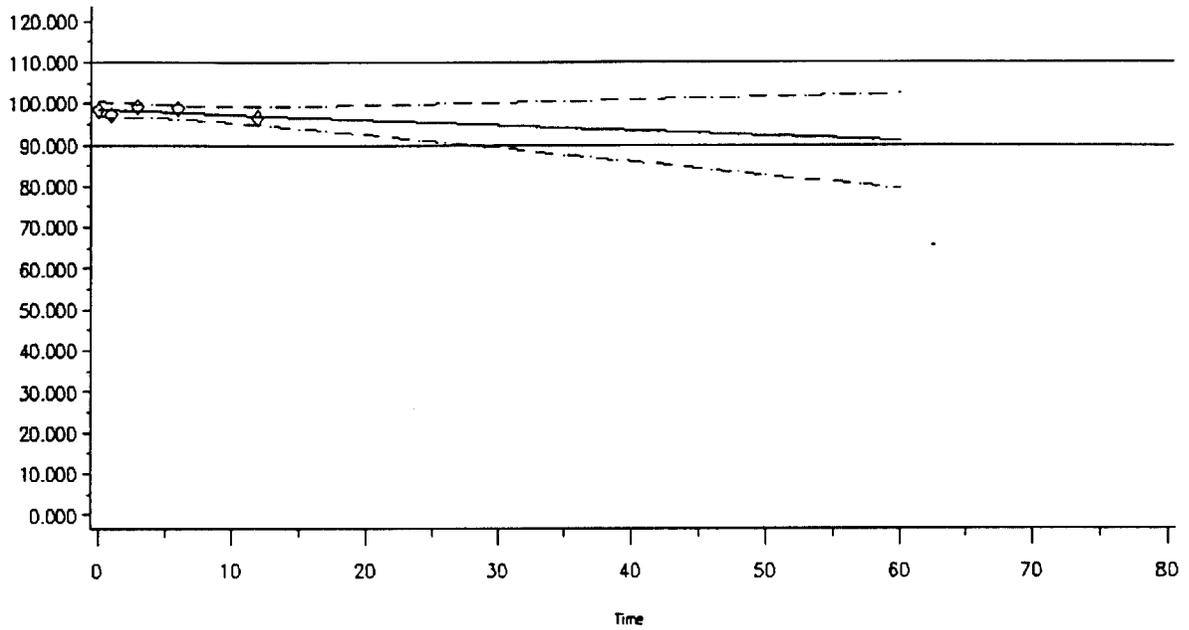
Figure 5. 95% Confidence Interval Plot for Batch CE54D

Stability Analysis

Variable Selected: ASSAY

Variable Type: Assay

BATCH NUMBER=CE54D



Legend: $\diamond \diamond \diamond$ Observed — Predicted - - - Upper CI - . - Lower CI

Type of Confidence Intervals: 95 x 2-Side CIs of Mean predicted values

Conclusion:

Expiration times were estimated from the data from three batches (5H099A, 5K072A, and CE54D). The minimum time, and thus the estimated expiry period, from these separate fits was 27 months.

 8/14/97
Steve Thomson
Mathematical Statistician, Biometrics IV

 08/14/97

Concur: R. Srinivasan, Ph. D.
Team Leader, Biometrics IV

~~ARCHIVE~~ NDA-20-743

HFD-540/Division File

HFD-540/Dr. Wilkin

HFD-540/Mr. Cross

HFD-725/Dr. Harkins

HFD-725/Dr. Srinivasan

HFD-725/Mr. Thomson

HFD-830/Dr. DeCamp

HFD-830/Dr. Higgins

HFD-344/Dr. Carreras

This review has eight pages with five figures.

Chron.

\\Thomson\WP Text\301\827-2078\August 12, 1997\c:\wpfiles\sta20743.wp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-743

MICROBIOLOGY REVIEW(S)

O. C. ...
540
AUG 19 1997

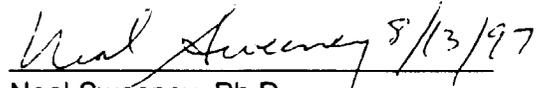
REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 3 of NDA 20-743
August 13, 1997

- A. 1. APPLICATION NUMBER: NDA 20-743
- APPLICANT: Dermik Laboratories
500 Arcola Road
Collegeville, PA 19426-0107
2. PRODUCT NAME: Noritate® (metronidazole 1% cream)
3. DOSAGE FORM: Metronidazole 1% topical cream in epoxy-coated aluminum tubes.
4. METHOD OF STERILIZATION: None (non-sterile product).
5. PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:
Metronidazole is an antibacterial and the proposed indication for Noritate (metronidazole 1% cream) is for the topical treatment of rosacea including inflammatory papules, pustules, and erythema. However, the applicant is not seeking an antimicrobial indication for Noritate.
6. DRUG PRIORITY CLASSIFICATION: 3S
- B. 1. DATE OF INITIAL SUBMISSION: September 30, 1997
2. DATE OF AMENDMENTS: 2/4/97 6/11/97 6/20/97
3. DATE OF CONSULTS: 2/19/97 6/20/97 7/28/97
4. ASSIGNED FOR REVIEW: 2/24/97 6/25/97 8/12/97
- C. REMARKS: Microbiologist's Review #1 (December 6, 1996) yielded one question (pertaining to microbial limits methodology and specifications) which was conveyed to the applicant on January 15, 1997 via FAX. Microbiological quality issues were clarified during a March 24, 1997 telecon with Kenneth Feld, Ph.D., Director, Dermik Product Development. This telecon resulted in the June 11, 1997 amendment. The applicant's satisfactory responses (Feb. 4, 1997 and June 11, 1997 amendments), the subject of Microbiologist's Review #2 resulted in a recommendation of approval (for issues concerning microbiological quality) of the drug product. The subject of Microbiologist's Review #3 is the applicant's July 28, 1997 amendment proposing a 24 month expiry.

D. CONCLUSIONS:

The proposed 24 month expiry is recommended for approval for issues concerning microbiological quality of the drug product, provided the applicant commit to supply updated 24 month microbial limits and preservative effectiveness stability data.


Neal Sweeney, Ph.D.

 8/19/97

cc:

Original NDA 20-743
HFD-540/ Division File
HFD-540/CSO/O. Cintron
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, August 13, 1997
R/D initialed by P. Cooney August 13, 1997

HFD 540/ C...

REVIEW FOR HFD-540

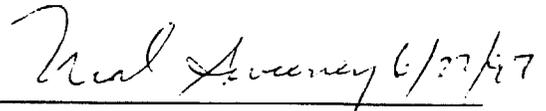
JUN 27 1997

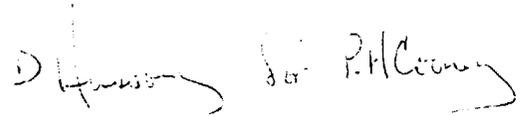
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 2 of NDA 20-743
June 27, 1997

- A. 1. APPLICATION NUMBER: NDA 20-743
- APPLICANT: Dermik Laboratories
500 Arcola Road
Collegeville, PA 19426-0107
- 2. PRODUCT NAME: Noritate® (metronidazole 1% cream)
- 3. DOSAGE FORM: Metronidazole 1% topical cream in epoxy-coated aluminum tubes.
- 4. METHOD OF STERILIZATION: None (non-sterile product).
- 5. PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:
Metronidazole is an antibacterial and the proposed indication for Noritate (metronidazole 1% cream) is for the topical treatment of rosacea including inflammatory papules, pustules, and erythema. However, the applicant is not seeking an antimicrobial indication for Noritate.
- 6. DRUG PRIORITY CLASSIFICATION: 3S
- B. 1. DATE OF INITIAL SUBMISSION: September 30, 1996
- 2. DATE OF AMENDMENTS: February 4, 1997 June 11, 1997
- 3. DATE OF CONSULTS: February 19, 1997 June 20, 1997
- 4. ASSIGNED FOR REVIEW: February 24, 1997 June 25, 1997
- C. REMARKS: Microbiologist's Review #1 (December 6, 1996) yielded one question which was conveyed to the applicant on January 15, 1997 via FAX. The applicant's responses (Feb. 4, 1997 and June 11, 1997 amendments) to the question are provided below and follow the italicized question from Microbiologist's Review #1. Microbiological quality issues were clarified during a March 24, 1997 telecon with Kenneth Feld, Ph.D., Director, Dermik Product Development. This telecon resulted in the June 11, 1997 amendment.

D. CONCLUSIONS:

The application is recommended for approval for issues concerning drug product microbial limits and preservative effectiveness testing.


Neal Sweeney, Ph.D.

 P. H. Cooney 6-27-97

cc:

Original NDA 20-743
HFD-540/ Division File
HFD-540/CSO/O. Cintron
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, June 27, 1997
R/D initialed by P. Cooney, June 27, 1997

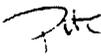
REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 1 of NDA 20-743
December 6, 1996

- A. 1. APPLICATION NUMBER: NDA 20-743
- APPLICANT: Dermik Laboratories
500 Arcola Road
Collegeville, PA 19426-0107
2. PRODUCT NAME: Noritate® (metronidazole 1% cream)
3. DOSAGE FORM: Metronidazole 1% topical cream in epoxy-coated aluminum tubes.
4. METHOD OF STERILIZATION: None (non-sterile product).
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
Metronidazole is an antibacterial and the proposed indication for Noritate (metronidazole 1% cream) is for the topical treatment of rosacea including inflammatory papules, pustules, and erythema. However, the applicant is not seeking an antimicrobial indication for Noritate.
6. DRUG PRIORITY CLASSIFICATION: 3S
- B. 1. DATE OF INITIAL SUBMISSION: September 30, 1996
2. DATE OF CONSULT: October 11, 1996
3. RELATED DOCUMENTS: (none)
4. ASSIGNED FOR REVIEW: October 28, 1996
- C. REMARKS: The consult request is for review of the microbial limit and preservative effectiveness testing for the drug product. This review also considers the microbiology aspects of the proposed stability protocol.

D. CONCLUSIONS:

The application is recommended as "approvable" for issues concerning drug product microbial limits and preservative effectiveness testing.

 12/6/96
Neal Sweeney, Ph.D.
 12/7/96

cc:

Original NDA 20-743
HFD-540/ Division File
HFD-540/CSO/O. Cintron
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, December 6, 1996
R/D initiated by P. Cooney December 6, 1996