CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-794

MICROBIOLOGY REVIEW

ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (DDDDP/HFD-540)

Clinical Microbiological Review #1

NDA#: 21-794 **REVIEW #:** 1 **COMPLETED DATE:** 06/20/05

SUBMISSION/TYPE	DOCUMENT DATE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
21-794 / Original PI	2571614	08/31/04	09/07/04	09/10/04
21-794 / Pivotal Studies	2615368	09/15/04	09/15/04	09/15/04
21-794 Micro Amendments	2660281	01/19/05	01/19/05	01/19/05
21-794 / Pivotal Studies	2666233	02/02/05	02/02/05	02/02/05
21-794 / Aczone™ PI	2671648	02/16/05	02/16/05	02/16/05
21-794 Sum. 203/204 / Microbiology	2692057	04/08/05	04/08/05	04/08/05

NAME & ADDRESS OF APPLICANT

Atrix Laboratories, Inc.
2579 Midpoint Drive
Fort Collins, CO 80525-4417
Tel: (970) 482-5868 / FAX: (970) 482-9734

CONTRACT PERSONS(s)

Cheri Jones, MS, RAC or
VP, Regulatory Affairs
Tel: (970) 212-4901
FAX: (970) 472-9734

Hansa Isokoski
QLT USA Inc.
Reg. Affairs Manager
Tel: (970) 212-4950 /
FAX: (970) 212-4974

SUBMISSION REVIEWED:

NDA 21-794 is submitted and reviewed for the support of the use of ACZONE™ GEL 5% for the topical treatment of acne vulgaris.

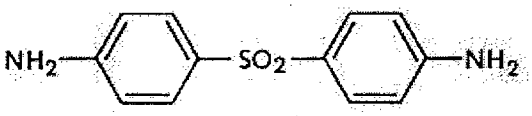
DRUG PRODUCT NAME:

Proprietary:	ACZONE™ (dapsone) GEL 5%
Nonproprietary/USAN:	dapsone
Code Names/#'s:	*NSC-6091* / DAPE / +DAPE
CAS Registry Number:	CAS-*80-08--0*

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. WT. (meropenem):

Chemical Name: Dapsone-USP, 4,4'-diaminodiphenylsulfone (DDS).

Structural Formula:



Molecular Formula	=	$C_{12}H_{12}N_2O_2S$
Molecular Weight	=	248.30

DOSAGE FORM: Aqueous gel

STRENGTH: 5% (50 mg/g) dapsone

ROUTE OF ADMINISTRATION: Topical

DISPENSED: _x_ Rx

PHARMACOLOGICAL CATEGORY:

Dapsone, a sulfone, has non-steroidal anti-inflammatory properties. The Applicant is not making any antibacterial labeling claims.

APPROVED INDICATION(s) / APPROVED DOSAGE AND ADMINISTRATION:

Dapsone is "approved" for the following indications:

1. Dermatitis herpetiformis: (D.H.); and
2. Leprosy: All forms of leprosy except for cases of proven dapsone resistance.

/ Dapsone is issued on prescription in tablets of 25 and 100 mg for oral use.

/ See current "approved" Dapsone labeling, under **DOSAGE AND ADMINISTRATION** section. Too much information to mention.

PROPOSED INDICATION:

ACZONE™ Gel 5% for the topical treatment of acne vulgaris.

PROPOSED DOSAGE AND ADMINISTRATION:

Apply a thin layer of ACZONE™ Gel 5% to the acne affected areas of skin twice daily after skin is gently washed and rub in gently and completely.

RELATED DOCUMENTS:

IND 54,440, SN 66, 10/28/02,

REMARKS / COMMENTS:

This is a Clinical Microbiology Review on NDA 21-794, ACZONE(dapsone) Gel 5% for the proposed topical treatment of acne vulgaris.

CONCLUSIONS:

There is no clinical microbiology studies conducted in the pivotal clinically studies.

Use of this proposed drug, ACZONE™ (dapsone) GEL 5% for the proposed topical treatment of

acne vulgaris is clinically driven.

CLINICAL MICROBIOLOGY LABELING

An "approval" letter should be issued to the Applicant, for NDA 21-794, after negotiation of their proposed "draft" Package Insert labeling with the FDA recommended **MICROBIOLOGY** section labeling and to read as follows:

MICROBIOLOGY

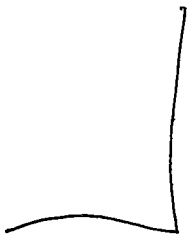


TABLE OF CONTENTS

EXECUTIVE SUMMARY
NDA 21-794 / ACZONE™ (dapsone) GEL 5%
(Atrix Laboratories, Inc. / QLT USA Inc.)

INTRODUCTION

The Applicant submits application, NDA 21-794, providing data for the proposed use of ACZONE™ (dapsone) GEL 5% for the topical treatment of acne vulgaris.

Acne is a common skin disease with onset in adolescence, characterized by papules, pustules, and comedones. The prevalence of acne is close to 100% of the population, with individuals differing only in severity of expression. Only 10% of adults recall ever having acne, but surveys among adolescents show more than an 80% incidence of manifest disease [1].

There are five intrinsic factors that contribute to the development of acne. These include:
1) sebum production, 2) hormone levels, 3) bacteria, 4) heredity, and 5) the predisposition of the individual to the disease, respectively. The pathogenesis of acne vulgaris is linked to androgens, bacteria, and "microbial inflammatory" mediators [2]. The predominant bacteria isolated in the follicular microbiota are the anaerobic gram positive pleomorphic bacilli *Propionibacterium acnes* (*P. acnes*). In 11–15 year olds without clinical acne, little or no *P. acnes* can be isolated from skin, whereas in adolescents with acne, the mean count is 1.1×10^5 bacteria/cm^2. It is hypothesized that *P. acnes* may release microbial inflammatory mediators, or trigger the release of cytokines from ductal keratinocytes that contributes to the disease pathogenesis.

Clinical improvement of acne occurs with antibiotics. However, the number of propionibacteria are not always diminished with systemic or topical antibiotic therapy, and the treatment of acne with broad spectrum antibiotics has generated concern about the likelihood of developing "resistant isolates". Isolates of *Propionibacterium* that are resistant to both tetracycline and doxycycline have been found in acne subjects. In addition to their antimicrobial properties, antibiotics may exhibit anti-inflammatory activity. This anti-inflammatory activity has been demonstrated for both tetracyclines and erythromycin [3].

Dapsone is a sulfone with both antimicrobial and anti-inflammatory properties [4,5]. Structurally, dapsone is similar to the sulfonamides, and the mechanism of antimicrobial action for both sulfones and sulfonamides is similar. These compounds are competitive inhibitors of dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of
para-aminobenzoic acid into dihydropteric acid, the immediate precursor of folic acid. Microorganisms that must synthesize their own folic acid are sensitive to this class of compounds, while bacteria that can utilize preformed folate are not affected [4].

Dapsone is shown to have some antibacterial activity against *P. acnes in vitro* [6]. The *in vitro* MIC_{90} of dapsone against 22 human skin isolates of *P. acnes* is 8 µg/mL.

The anti-inflammatory properties of dapsone appear unrelated to its capacity to interfere with the synthesis of folic acid in susceptible microorganisms. Dapsone may inhibit the myeloperoxidase-based and hydrogen peroxide-based cytotoxic system of neutrophils, or dapsone may act as a scavenger of reactive oxygen species, thereby minimizing inflammation associated with the generation of these reactive species [5]. With dual antimicrobial and anti-inflammatory mechanisms of action, topical dapsone may be of significant benefit to patients with acne.

PRECLINICAL EFFICACY (*IN VITRO*)

MICROBIOLOGY

Mechanism of Action
The etiology and pathogenesis of acne are not completely understood, but the key steps appear to be the formation of a microcomedone and its progression to the inflammatory lesions of severe acne [7]. The mechanism by which dapsone exerts it efficacy in the treatment of acne is unknown, but it is thought to result from a combination of both it anti-inflammatory and antimicrobial activities [8].

a. Anti-inflammatory
Some of the non-clinical anti-inflammatory properties of dapsone include: a) inhibition of neutrophil myeloperoxidise and eosinophil peroxidase and suppression of hypochlorous acid production [9], b) dapsone scavenges reactive oxygen species and minimizes inflammation associated with the generation of these highly reactive species [10], dapsone suppresses neutrophil recruitment and local production of toxic respiratory and secretory products and inhibits chemoattractant-induced signal transduction [11].

b. Antimicrobial
The antimicrobial activity of dapsone is unrelated to its anti-inflammatory activity. Dapsone competitively inhibits dihydropteroate synthase, the bacteria enzyme responsible for the incorporation of para-aminobenzoic acid into dihydropteric acid, the immediate precursor of folic acid [12]. Microorganisms that need to synthesize their own folic acid are sensitive to this class of compounds.

In Vivo Activity
No microbiology or immunology studies were conducted during the dapsone gel clinical trials.

Drug Resistance
No resistance studies were conducted during the dapsone gel clinical trials. Therapeutic resistance to dapsone has been reported in *Mycobacterium leprae* during oral treatment with dapsone [13].

Drug to Drug Interactions
In vitro, there may be potentially synergism (decreased MICs) when dapsone is used in combination with trimethoprim; however, the clinical significance is unknown [14].

MICROBIOLOGY STUDY / REPORT RESULTS

"Study Synopsis: Study DAP9907 A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5%. Dapsone Topical Gel and Vehicle Control in Normal Subjects". Study Number: DAP 9907.
Study Title: "A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and Vehicle Control in Normal Subjects"

From a Microbiological perspective, it is difficult to make any definitive conclusions between the 5% DTG dapsone gel and the Vehicle Control test groups on the exploratory study results in the reduction of the *Propionibacterium* bacterial counts in healthy patients..

The percentage reduction of the *Propionibacterium* bacterial overlap over each other. The 5% DTG formulation reduces the *Propionibacterium* bacterial counts from Baseline 63% to 70% and The Vehicle Control reduces the *Propionibacterium* bacterial counts by 54% to 78%.

The Applicants explains that the failure to detect a difference between 5% DTG and Vehicle Control groups

may be due to the small sample size and/or the higher *Propionibacterium* bacterial counts in patients randomized to the Vehicle Control group at Baseline.

The commercial or marketed Dapsone Gel %5 is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily." In this exploratory evaluation study, the gel is applied only to the forehead.

In Vitro SUSCEPTIBILITY
(eNDA 21-794, Document 2692057, Module 2.7.6, 5% DAPSONE TOPICAL GEL, MODULE 2.7.6.18, SYNOPSES OF INDIVIDUAL STUDIES, 040805.pdf, page 79)

"Study Synopsis: 51201 Summary of Reports 51197, 51198, 51199, and 51200: Antimicrobial Susceptibility of *Propionibacterium Acnes* to Dapsone"

Study Number: 51202 (Summary Reports: 51197, 51198, 51199, and 51200, respectively.)
Purpose:
Susceptibility testing of dapsone against *Propionibacterium acnes* and other anaerobic and aerobic bacteria is conducted to evaluate its potential antimicrobial activity in the treatment of acne.

In a non-clinical program for dapsone, the *in vitro* antimicrobial activity of dapsone and other antimicrobials is evaluated against American Type Culture Collection (ATCC) reference stains of the anaerobic bacteria *Propionibacterium acnes*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Eubacterium lentum*, and aerobic bacteria *Staphylococcus aureus* and *Escherichia coli* by minimum inhibitory concentration (MIC) testing. In addition to the reference stains of *Propionibacterium acnes*, clinical isolates of *Propionibacterium acnes* are also tested.
Conclusions:
Dapsone has some activity (i.e., MIC Range = 4 to 16 µg/mL) against *Propionibacterium acnes* and *Propionibacterium* species. However, the effectiveness of dapsone in treating acne vulgaris due to the aforementioned microorganisms (i.e., essentially *Propionibacterium acnes*) has not been established in adequate and well-controlled trials.

The Applicant's expects the topical application of dapsone to the affected skin will result in locally high concentrations of dapsone; many-fold higher than the MIC_{90} found in this study. The Dapsone Gel 5% is designed to maintain high level dapsone concentrations in the outer layers of the stratum corneum and in the opening of the follicle (pilosebaceous canal) in which *Propionibacterium* species and *Propionibacterium acnes* may reside. The higher concentration of dapsone is expected by the Applicant to contribute to the efficacy of the drug in the treatment of acne.

However, the microbiology susceptibility results and conclusions are problematic. This Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) procedure is not recognized by the Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards (NCCLS) organization.

Clinical MICROBIOLOGY LABELING

An "approval" letter should be issued to the Applicant, for NDA 21-794, after negotiation of their proposed "draft" Package Insert labeling with the FDA recommended **MICROBIOLOGY** section labeling and to read as follows:

MICROBIOLOGY

In Vivo Activity:
No microbiology or immunology studies were conducted during dapsone gel clinical trial.

Drug Resistance:
No dapsone resistance studies were conducted during dapsone gel clinical trials. Therapeutic resistance to dapsone has been reported in *Mycobacterium leprae* oral treatment with dapsone [13].

BIBLIOGRAPHY

[1] Plewig G. and A.M. Kligman. Acne and Rosacea. Springer-Verlag. New York. 1993.

[2] Harper J.C. and D. Thiboutot. Pathogenesis of Acne: Recent Research Advances. Adv. Dermatol. 2003;19:1-10.

[3] Jape U. Pathological Mechanisms of Acne with Special Emphasis on *Propionibacterium acnes* and Related Therapy. Acta. Derm. Venereol. 2003; 83:241-248.

[4] Mandell G.L. and M.A. Sande. Antimicrobial Agents. Gilman A.G., Rall T.W., Nies A.S., and P. Taylor, Eds. The Pharmacological Basis of Therapeutics. Eighth Edition. New York: Pergamon Press. 1990;1048.

[5] Wozel G. and J. Barth. Current Aspects of Modes of Action of Dapsone. Intl. J. Derm. 1988;27(8):547-552.

[6] Data on File at Atrix Laboratories. Laboratory Notebook: KG1064-18.

[7] Jeremy A.H., Holland D.B., Roberts S.G., Thomson K.F. and W.J. Cunliffe. Inflammatory Events are Involved in Acne Lesion Initiation. J. Invest. Dermatol. 2003;121(1):20-27.

[8] Paniker U. and N. Levine. Dapsone and Sulfapyridine. Dermtol. Clin. 2001;19(1):79-86.

[9] Kazmierowski J.A., Ross J.E., Peizner D.S., and K.D. Wuepper. Dermatitis herpetiformis: effects of sulfones and sulfonamides on neutrophil myeloperoxidase-mediated iodination and cytotoxicity. J. Clin. Immunol. 1984;4(1):55-64.

[10] Maloff B.L., Fox D., Burin E., and T.M. Di Meo. Dapsone Inhibits LTB_4 Binding and Bio-response at the Cellular and Physiologic Levels. Eur. J. Pharmacol. 1988;158(1-2):85-89.

[11] Debol S.M., Herron M.J., and R.D. Nelson. Anti-inflammatory Action of Dapsone: Inhibition of Neutrophil Adherence is Associated with the Inhibition of Chemoattractant-induced Signal Transduction. J. Leukoc. Biol. 1997;62(6):827-836.

[12] Coleman M.D. Dapsone: Modes of Action, Toxicity and Possible Strategies for Increasing Patient Tolerance. Br. J. Dermatol. 1993:129:507-513.

[13] Matsuoka, M. A. Dec 2000. *Mycobacterium leprae* isolate resistant to dapsone, rifampin, ofloxacin and sparfloxacin. Int J Lepr Other Mycobact Dis. 68(4):452-5.

[14] MICROBIOLOGY REPORT 51200: Improvement of Dapsone MIC by Synergism with Trimethoprim.

Appendix 3 Micro. Report 51200: Module 5, Vol. 117. August 25, 2004.

CLINICAL MICROBIOLOGY REVIEW

I. INTRODUCTION

The Applicant submits application, NDA 21-794, providing data for the proposed use of ACZONE™ (dapsone) GEL 5% for the topical treatment of acne vulgaris.

Acne is a common skin disease with onset in adolescence, characterized by papules, pustules, and comedones. The prevalence of acne is close to 100% of the population, with individuals differing only in severity of expression. Only 10% of adults recall ever having acne, but surveys among adolescents show more than an 80% incidence of manifest disease [1].

There are five intrinsic factors that contribute to the development of acne. These include: 1) sebum production, 2) hormone levels, 3) bacteria, 4) heredity, and 5) the predisposition of the individual to the disease, respectively. The pathogenesis of acne vulgaris is linked to androgens, bacteria, and "microbial inflammatory" mediators [2]. The predominant bacteria isolated in the follicular microbiota are the anaerobic gram positive pleomorphic bacilli *Propionibacterium acnes* (*P. acnes*). In 11–15 year olds without clinical acne, little or no *P. acnes* can be isolated from skin, whereas in adolescents with acne, the mean count is 1.1×10^5 bacteria/cm^2. It is hypothesized that *P. acnes* may release microbial inflammatory mediators, or trigger the release of cytokines from ductal keratinocytes that contributes to the disease pathogenesis.

Clinical improvement of acne occurs with antibiotics. However, the number of propionibacteria are not always diminished with systemic or topical antibiotic therapy, and the treatment of acne with broad spectrum antibiotics has generated concern about the likelihood of developing "resistant isolates". Isolates of *Propionibacterium* that are resistant to both tetracycline and doxycycline have been found in acne subjects. In addition to their antimicrobial properties, antibiotics may exhibit anti-inflammatory activity. This anti-inflammatory activity has been demonstrated for both tetracyclines and erythromycin [3].

Dapsone is a sulfone with both antimicrobial and anti-inflammatory properties [4,5]. Structurally, dapsone is similar to the sulfonamides, and the mechanism of antimicrobial action for both sulfones and sulfonamides is similar. These compounds are competitive inhibitors of dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of para-aminobenzoic acid into dihydropteric acid, the immediate precursor of folic acid. Microorganisms that must synthesize their own folic acid are sensitive to this class of compounds, while bacteria that can utilize preformed folate are not affected [4].

Dapsone is shown to have some antibacterial activity against *P. acnes in vitro* [6]. The *in vitro* MIC_{90} of dapsone against 22 human skin isolates of *P. acnes* is 8 µg/mL. [See a discussion on Study Number: DAP 9907, Study Synopsis: **Study DAP9907 A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and Vehicle Control in Normal Subjects,** in this review.]

The anti-inflammatory properties of dapsone appear unrelated to its capacity to interfere with the synthesis of folic acid in susceptible microorganisms. Dapsone may inhibit the myeloperoxidase-based and hydrogen peroxide-based cytotoxic system of neutrophils, or dapsone may act as a

scavenger of reactive oxygen species, thereby minimizing inflammation associated with the generation of these reactive species [5]. With dual antimicrobial and anti-inflammatory mechanisms of action, topical dapsone may be of significant benefit to patients with acne.

II. PRECLINICAL EFFICACY (*IN VITRO*)

MICROBIOLOGY

Mechanism of Action

The etiology and pathogenesis of acne are not completely understood, but the key steps appear to be the formation of a microcomedone and its progression to the inflammatory lesions of severe acne [7]. The mechanism by which dapsone exerts it efficacy in the treatment of acne is unknown, but it is thought to result from a combination of both it anti-inflammatory and antimicrobial activities [8].

a. Anti-inflammatory

Some of the non-clinical anti-inflammatory properties of dapsone include: a) inhibition of neutrophil myeloperoxidise and eosinophil peroxidase and suppression of hypochlorous acid production [9], b) dapsone scavenges reactive oxygen species and minimizes inflammation associated with the generation of these highly reactive species [10], dapsone suppresses neutrophil recruitment and local production of toxic respiratory and secretory products and inhibits chemoattractant-induced signal transduction [11].

b. Antimicrobial

The antimicrobial activity of dapsone is unrelated to its anti-inflammatory activity. Dapsone competitively inhibits dihydropteroate synthase, the bacteria enzyme responsible for the incorporation of para-aminobenzoic acid into dihydropteric acid, the immediate precursor of folic acid [12]. Microorganisms that need to synthesize their own folic acid are sensitive to this class of compounds.

In Vivo Activity

No microbiology or immunology studies were conducted during the dapsone gel clinical trials.

Drug Resistance

No resistance studies were conducted during the dapsone gel clinical trials. Therapeutic resistance to dapsone has been reported in *Mycobacterium leprae* during oral treatment with dapsone [13].

Drug to Drug Interaction

In vitro, there may be potentially synergism (decreased MICs) when dapsone is used in combination with trimethoprim; however, the clinical significance unknown [14].

III. CLINICAL STUDIES

The Applicant performed 2-pivotal clinical studies, DAP 203 and DAP 204. See Table 1.

However, the 2 pivotal studies, DAP 203 and DAP 204, are identically designed with respect to objective, procedures, treatment duration, endpoints, and statistical analyses. Therefore, only Clinical Study DAP 203 is fully discussed.

Table 1* show summaries on the pivotal Clinical Studies DAP 203 and DAP 204.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Exposure	Study Status; Type of Report
Controlled, Pertinent to the clinical indication	DAP0203	Mod 5 Vol 17-40	To compare the safety and efficacy of 5% DTG versus vehicle control applied twice daily for the treatment of acne vulgaris	Phase 3, multicenter, double-blind, randomized, parallel design study	5% Dapsone/ 25% DGME or 25% DGME (topical)	Planned 1450; Enrolled 1485; Completed 1255; Discontinued 230	Patients with acne vulgaris	Applied twice daily for 12 weeks	Complete; Full Report
Controlled, Pertinent to the clinical indication	DAP0204	Mod 5 Vol 41-65	To compare the safety and efficacy of 5% DTG versus vehicle control applied twice daily for the treatment of acne vulgaris	Phase 3, multicenter, double-blind, randomized, parallel design study	5% Dapsone/ 25% DGME or 25% DGME (topical)	Planned 1450; Enrolled 1525; Completed 1253; Discontinued 272	Patients with acne vulgaris	Applied twice daily for 12 weeks	Complete; Full Report

* Adapted from eNDA 21-794, eDocument 2660281 Dated: 01/19/05, Atrix Laboratories, Inc., AMEND01 Module 2.7.6, 01.14.05pdf, 5% Dapsone Topical Gel, Protocol Number DAP 9907, Amendment 01, Dated: 01/14/05.

SUMMARY of CLINICAL STUDY DAP 203 (DAP 204)

Name & Address of Applicant:
Atrix Laboratories, Inc., 2579 Midpoint Drive, Fort Collins, CO 80525
Phone: 800-442-8749 / Fax: 970-482-9734

Clinical Analyses:
Clinical laboratory analyses are performed at a central laboratory (

Clinical Photographs:
Photographs to document disease status are taken at five study centers:

Study ID: DAP203

Study / Drug Rationale:
The development plan for topical dapsone provides for a formulation that that is expected to result in clinically effective concentrations of drug delivered to the skin while minimizing systemic absorption and the associated adverse events describe with oral dapsone treatment.

Protocol Title:
"A 12-Week, Multicenter, Double-Blind, Randomized, Parallel-Design Study of 5% Dapsone Topical Gel and Vehicle Control in Patients with Acne Vulgaris."

Study Objectives:
To determine the efficacy and safety of twice daily applications of 5% Dapsone Topical Gel (DTG) in patients with acne vulgaris.

Study Design:
This is a multicenter, double-blind, randomized, parallel group, 2-arm, vehicle-controlled design study in which patients are randomized to receive either 5% formulation Dapsone Topical Gel (DTG) or Vehicle Control (VC) twice daily for 12 weeks to evaluate the efficacy and safety of 5% Dapsone Topical Gel for the treatment of acne vulgaris.

Study Initiation Date:	November 18, 2002
Study Completion Date:	August 15, 2003
Date of Report:	May 14, 2004

Study Sites: United States and Canada.

Study Period: 12 Weeks

Number of Patients:
A total of approximately 1450 patients are randomized in this study; 725 to the DTG group and 725 to the VC group.

Gender: Male and female.
Age: 12 years of age or older

Inclusion:
Clinical diagnosis of acne vulgaris of the face, with 20 to0 50 inflammatory lesions and 20 to 100 non-inflammatory lesions above the mandibular line at Baseline..

Test Articles: 5% Dapsone Topical Gel (DTG) and Vehicle Control (VC), respectively.
Both products are dispensed in [redacted] co-extruded 30-gram (g) tubes with white ribbed caps.

Manufacturer:
The test articles are manufactured, prepared, and supplied by Atrix Laboratories, 701 Centre Avenue Fort Collins, CO 80526 USA.
A third party distribution center, [redacted], is responsible for labeling, distributing, and tracking the return of all test articles.

Lot Numbers:
The lot numbers of DTG in this study are 1555 and 1617. The lot numbers of VC are 1541, 1554, and 1616, respectively.

Mode of Administration:
The test article is applied after the skin is thoroughly washed with a non-comedogenic (soap-free) cleanser, rinsed with warm water, and gently patted dry. A standard soap-free cleanser is provided to all, study participants.
Patients apply a thin film of randomized test article to the face twice daily (once in the morning and once in the evening at least 1 hour prior to bedtime) for 12 weeks. Patients are also allowed to treat other acne-affected areas, however, these areas are not assessed for efficacy.

The test article is gently rubbed in until it completely disappeared. The patient checks a box next to "AM" or "PM" on the application log to indicate that they apply the test article.

Primary Variables of Interest:
The **primary** efficacy variables evaluated in the study are Global Acne Assessment Score (GAAS) and mean percent reduction in acne lesion counts.

Efficacy evaluations consist of the Global Acne Assessment Score (GAAS) and the number of inflammatory, non-inflammatory, and total acne lesions. Efficacy evaluations, including the (GAAS) and acne lesion counts, are performed on the face at Screening/Baseline, and then repeated at Weeks 2, 4, 6, 8, 12 and early termination (ET).

A subset of patients have photographs of the face taken to document clinical response at Baseline and Weeks 4, 8, and 12.

Figure 1* shows a schematic overview/outline of the study procedures.

Assessment	Baseline (Day 0)	Weeks 2, 4, 6, 8	Week 10	Week 12[a]
Informed consent	X			
Admission criteria	X			
Demographics	X			
Medical history	X			
Vital signs	X			X
Pregnancy status	X			X
Physical examination	X			X
Height and weight	X			
Hematology[b]/serum chemistry blood draw	X			X
Global Acne Assessment	X	X		X
Acne lesion counts	X	X		X
Local Reaction Assessment	X	X		X
Photographs of the skin[c]	X	X[d]		X
Test article application instructions/compliance	X	X	X	X
Adverse events and procedures		X	X	X
Concomitant medication	X	X	X	X

* Adapted from eNDA 21-794, eDocument 2615368, Atrix Laboratories, Inc., Report DAP 203, 5. **INVESTIGATIONAL PLAN**, 5.1 **Overall Study Design and Plan-Description**, Figure A, Page 5, Dated: 09/15/04.

[a] Week 12 or early termination (ET).
[b] G-6-PD analysis at Baseline only.
[c] At a chosen subset of study centers only.
[d] Weeks 4 and 8 only.

Criteria for Evaluation:
The objective of the study is to determine the efficacy and safety of 5% DTG. Efficacy of DTG relative to VC is determined at Week 12/ET by the incidence of Success (GAAS of 0 or 1), as well as the mean percent reduction in inflammatory, non-inflammatory, and total acne lesion counts. The efficacy criteria of the study are met if results from the DTG group are significantly better than those observed in the VC group for:

- Success based on GAAS, and
- Mean percent reduction in two of the three acne lesion count parameters.

Clinical Results, Discussion, Recommendations, and Conclusions:

See FDA/DDDDP/HFD-540 Medical Officer's Clinical Review.

IV. MICROBIOLOGY STUDIES

(eNDA 21-794, Document 2692057, Module 2.7.6, 5% DAPSONE TOPICAL GEL, MODULE 2.7.6.17, SYNOPSES OF INDIVIDUAL STUDIES, 040805.pdf, page 76)

"Study Synopsis: Study DAP9907 A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and Vehicle Control in Normal Subjects"

Study Number: DAP 9907

Study Title:
"A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and Vehicle Control in Normal Subjects"

Test Drugs:
5% dapsone topical gel (DTG) formulation and a vehicle control (VC).

Test Product, Dose and Mode of Administration, Batch Number:
The test articles are manufactured, prepared and supplied by Atrix Laboratories. The 5% DTG used in the study is a smooth gel formulation.

The lot number of the 5% DTG is NBBP-A, and the lot number of the vehicle control is 019-98.

Study Design:
Study DAP9907 is a 10-week, single center, single-blind, randomized parallel-design, microbiological study in which 20 patients received daily applications of either 5% DTG or vehicle control to their foreheads for up to 8 weeks.

Microbiology Inclusions:
Patients with at least 10^5 colony forming units (CFU) / cm^2 of *Propionibacterium* species, which may include *Propionibacterium acnes*, on their center forehead.

Study Objective:
The Primary Objective of this study is to compare the bacterial counts of *Propionibacterium* species, which may include *Propionibacterium acnes*, on the skin of subjects following once daily application of either 5% DTG or its Vehicle Control. This is an exploratory evaluation.

Study Randomization:
All patients are randomized to receive either 5% DTG or vehicle control in accordance with a computer-generated table.

Drug Administration:
Approximately 250 mg of test article, either 5% DTG formulation or vehicle control, are rubbed gently, once daily, onto the forehead (approximately 50 cm^2), beginning with the middle and working outwards. The product is rubbed in until it completely disappeared.

Study Variable:
The Primary Variable of interest in this study is to compare the bacterial counts of *Propionibacterium* species, which may include *Propionibacterium acnes,* following daily application of either 5% DTG or vehicle control. Safety is determined by standard clinical research methods.

Number of Patients (Planned and Analyzed):
Up to 20 patients are planned for enrollment in the 5% DTG treatment group and up to 10 patients in the vehicle control treatment group.

Because of difficulties with recruiting patients that meet the entry criteria, Fourteen (14) 5% DTG and 6 vehicle control patients are actually enrolled in the study. Sample size is based on having a reasonable number of patients for an exploratory evaluation comparing bacterial counts of *Propionibacterium* species, which may include *Propionibacterium acnes* between Baseline and on-study time points, as well as between treatment groups.

Gender / Age:
Patients are healthy males or females, age 18 to 40 years.

Duration of Treatment:
Each patient is exposed to approximately 250 mg of either 5% DTG formulation or the vehicle control once daily for 8 weeks.

Microbiology Criteria for Evaluation:
The outcome measure in this study is the difference between Baseline and on-study time points in bacterial counts of *Propionibacterium* species, which may have included *Propionibacterium acnes,* following daily application of either 5% DTG or vehicle control.

Samples are collected for microbiological analysis (bacterial counts) at Pre-Screening, Baseline, and Weeks 2, 4, 6, 8, 9, and 10, and analyzed.

Microbiology Results:
The range of *Propionibacterium* species bacterial counts observed is as follows:

At Baseline is 113,821 CFU/cm² to 11,222,222CFU/cm² in the 5% DTG-treated patients (median 1,332,964 CFU/cm²); and
It is 2,682,926 CFU/cm² to 4,715,477 CFU/cm²) for the Vehicle Control-treated patients (median 3,739,837 CFU/cm²).

Intent-To-Treat (ITT) Population:

Results at the end of treatment (Week 8) of the study demonstrate a reduction in the *Propionibacterium* species bacterial counts ranging from 63% to 70% in the DTG test group; and
It is a 54% to 78% bacterial counts reduction in the Vehicle Control group.

Per Protocol (PP) Population:

The reduction in *Propionibacterium* species bacterial counts range from 64% to 71% in the 5% DTG group; and
It is 39% to 77% bacterial counts reduction in the Vehicle Control group.

NOTE: (also See DAP9907 Study Report, Module 5.3.5.4.2)

Conclusions:
From a Microbiological perspective, it is difficult to make any definitive conclusions between the 5% DTG dapsone gel and the Vehicle Control test groups on the exploratory study results in the reduction of the *Propionibacterium* bacterial counts in healthy patients.

The percentage reduction of the *Propionibacterium* bacterial counts lap over each other. The 5% DTG formulation reduces the *Propionibacterium* bacterial counts from Baseline 63% to 70% and The Vehicle Control reduces the *Propionibacterium* bacterial counts by 54% to 78%.

The Applicants explains that the failure to detect a difference between 5% DTG and Vehicle Control groups may be due to the small sample size and/or the higher *Propionibacterium* bacterial counts in patients randomized to the Vehicle Control group at Baseline.

The commercial or marketed Dapsone Gel %5 is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily." In this exploratory evaluation study, the gel is applied only to the forehead.

In Vitro SUSCEPTIBILITY

(eNDA 21-794, Document 2692057, Module 2.7.6, 5% DAPSONE TOPICAL GEL, MODULE 2.7.6.18, SYNOPSES OF INDIVIDUAL STUDIES, 040805.pdf, page 79)

"Study Synopsis: 51201 Summary of Reports 51197, 51198, 51199, and 51200: Antimicrobial Susceptibility of *Propionibacterium Acnes* to Dapsone"

Study Number: 51202 (Summary Reports: 51197, 51198, 51199, and 51200, respectively.)

Microbiology Report 51197:
"Determination of the Minimum Inhibitory Concentration (MIC) of Clindamycin, Doxycycline, Erythromycin, Gentamicin, Metronidazole, Penicillin, and Sulfisoxazole for Reference Stains and Human Isolates of *Propionibacterium acnes* and other Bacterial Reference Strains"

Microbiology Report 51198:
"Use of Spiral Gradient Endpoint (SGE) in the Determination of Susceptibility to Dapsone and Certain Other Antimicrobials by Clinical Isolates of *Propionibacterium* and ATCC Strains of *Propionibacterium acnes"*

Microbiology Report 51199:
"Susceptibility of *Propionibacterium* Species and Other Bacteria to Certain Antimicrobials including Dapsone by use of Four Methodologies and Initial Studies of Dapsone and Trimethoprim Synergy"

NOTE: 1) Used same isolates as reported in 51197,
2) Parts of this report is a reiteration of Report 51200

Purpose:
Susceptibility testing of dapsone against *Propionibacterium acnes* and other anaerobic and aerobic bacteria is conducted to evaluate its potential antimicrobial activity in the treatment of acne.

In a non-clinical program for dapsone, the *in vitro* antimicrobial activity of dapsone and other antimicrobials is evaluated against American Type Culture Collection (ATCC) reference stains of the anaerobic bacteria *Propionibacterium acnes*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Eubacterium lentum*, and aerobic bacteria *Staphylococcus aureus* and *Escherichia coli* by minimum inhibitory concentration (MIC) testing. In addition to the reference stains of *Propionibacterium acnes*, clinical isolates of *Propionibacterium acnes* are also tested.

Study Title:
"Study Synopsis: 51201 Summary of Reports 51197, 51198, 51200, and 51199 Antimicrobial Susceptibility of *Propionibacterium Acnes* to Dapsone".

Test Drug: An aqueous gel containing 5% dapsone in 25% DGME.

Study Rationale:
Dapsone possesses both antibacterial and anti-inflammatory properties which, when combined with appropriate solvents, makes it an attractive candidate for acne therapy. Considering its long history as an antimicrobial agent, efforts began to quantify the susceptibility of *Propionibacterium acnes* to dapsone.

Study Drug Dose Rationale:
In vitro studies including skin transport studies are used to optimize the concentrations of dapsone and appropriate solvents for use in clinical trials. An aqueous gel containing 5% dapsone in 25% DGME is found to be the optimum candidate.

Isolates Tested:
A total of 43 clinical isolates of *Propionibacterium* species are tested.

Antimicrobial susceptibility testing with dapsone and other antimicrobials are performed on 22 *Propionibacterium* isolates (including 20 *Propionibacterium acnes* isolates) isolated from normal (i.e., healthy) volunteers.

An additional 21 P*ropionibacterium* isolates (including 9 *Propionibacterium acnes* isolates) isolated from patients with acne, obtained from a research laboratory at the I [redacted]

Therefore, of the total 43 *Propionibacterium* species, 29 (67.4%) are *Propionibacterium acnes.*

Methodology*:
The procedure for collection, identification (Gram stain, biochemical testing, e.g., "Biolog Biochemical Bacterial Identification System" – purple color dye reaction), growth requirements, and MIC testing of clinical isolates of *Propionibacterium* are described.

Susceptibility (MIC) Testing:
Testing for antimicrobial activity is conducted and evaluated using 1) a Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) method, 2) CLSI / NCCLS* broth microdilution method (MICs), 3) CLSI / NCCLS cylinder plate diffusion (zone diameters -- mm), and 4) growth curve/time-kill susceptibility methodology.

The "spiral gradient endpoint" (SGE) methodology is used to determine antimicrobial susceptibility. It uses a gradient of drug concentration created on a single agar plate to which bacteria are radially plated across the drug gradient.

*NOTE: The Clinical and Laboratory Standards Institute (CLSI) is the new name for the former National Committee for Clinical Laboratory Standards (NCCLS) organization.

Quality Control / Reference Strains:
Quality Controls and Reference Strains are used and identified.

Results:
Among these assays, the Applicant determined that the Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) technique is more accurate, reproducible endpoints, less time- and labor-intensive, and subject to less interpretative error than the other tested methods. The CLSI / NCCLS test methods are not used because of technical difficulties.

Using the Applicant's SGE-MIC method on the 22 *Propionibacterium* isolates (including 20 *Propionibacterium acnes* isolates) from normal human subjects, the MIC_{90} is found to be 8 µg/mL.

The additional [redacted] research laboratory 21 *Propionibacterium* species (including 9 *Propionibacterium acnes*) isolated from patients with acne, tested by the Applicant's SGE-MIC procedure, had MIC values in the range of 4 to 8µ/mL.

Microbiology Report 51198:
"Use of Spiral Gradient Endpoint (SGE) in the Determination of Susceptibility to Dapsone and Certain Other Antimicrobials by Clinical Isolates of *Propionibacterium* and ATCC Strains of *Propionibacterium acnes"*

The applicant states under **CONCLUSIONS:** "Five isolates of *Propionibacterium* were relatively resistant to dapsone: E116, C779, 691, 710, and 728".

If one looks at the Applicant's Table 3, on pages 18 to 21, the Applicants states "....while 1 strain 11827 appears resistant". *Propionibacterium acnes* ATCC 25746 and 29399 are also a concern for resistance and precise susceptibility results among others.

Conclusions:
Dapsone has some activity (i.e., MIC Range = 4 to 16 µg/mL) against *Propionibacterium acnes* and *Propionibacterium* species. However, the effectiveness of dapsone in treating acne vulgaris due to the aforementioned microorganisms (i.e., essentially *Propionibacterium acnes*) have not been established in adequate and well-controlled trials.

The Applicant's expects the topical application of dapsone to the affected skin will result in locally high concentrations of dapsone; many-fold higher than the MIC_{90} found in this study. The higher concentration of dapsone is expected by the Applicant to contribute to the efficacy of the drug in the treatment of acne.

However, the microbiology susceptibility results and conclusions are problematic. This Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) procedure is not recognized by CLSI / NCCLS.

NOTE:
The Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) is unacceptable at this time.

The following analysis explanation is one of the reasons the Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) procedure is yet to be recognized and accepted as a standard MIC method":

The MICs obtained by the SGE method are continuous and discrete rather than incremental twofold dilution steps. The continuous or actual concentration at which inhibition occurred, termed the tail-ending concentration (TEC), is used as one of the SGE test endpoints. However, for a more direct comparison with the standard agar dilution SAD method values, each TEC growth endpoint concentration of the SGE test is rounded up to the next higher twofold dilution value corresponding to that of the SAD method series. Thus, if TEC was 1.8 µg/mL, the SGE or gradient MIC (GMIC) would be 2 µg/mL; this presents the data in another form which are equivalent to the incremental MIC by the SAD method, The GMIC previously was termed the SGE- MIC.

Also, it is shown in one of the references articles[15], if TEC is 1.10 or 2.2 µg/mL, the SGE or gradient MIC (GMIC) is 2.00 and 4.00 µg/mL, among many other values, respectively. The rounding up of such values is questionable and is a concern among authoritative susceptibility testing Microbiologists and other scientific disciplines

MICROBIOLOGY REPORT 51200

Improvement of Dapsone MIC by Synergism with Trimethoprim / August 25, 2004

Purpose:
To investigate the potential synergism between dapsone and trimethoprim. To determine the MIC of dapsone and trimethoprim (folate pathway inhibitor) in combination using *Propionibacterium*

acnes ATCC 6919 and other clinical isolates.

The appropriate ratio of dapsone to *Propionibacterium acnes* trimethoprim is determined with the type stain, followed by clinical isolates of *Propionibacterium*, including *Propionibacterium acnes* that previously tested resistant to dapsone.

Rationale:
The Applicant mentions that the SGE-MIC methodology is capable of measuring the MIC of drug combinations mixed together in specific ratios in calculated concentrations.

Trimethoprim is a folate pathway inhibitor. It is a synthetic antibiotic that interferes with the production of folic acid, a critical compound in many bacteria as well as humans. Trimethoprim inhibits production of folic acid by binding to the enzyme responsible for making folic acid and blocking the enzyme from making folic acid.

Methodology:
The Applicant's Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) test method is used to measure susceptibility to antibiotics and to determine antagonistic, additive, or synergistic interactions between dapsone and trimethoprim. This methodology is relevant to the "Checkerboard Method" [16].

Bacterial Strains:
Propionibacterium acnes - Strains:

ATCC 6919, ATCC 11827, ATCC 29399: 8,14, 23, 35, and E116, and
(The "8, 14".... refers to the isolate identification.)
Propionibacterium species – Strains: 17, C779, 691, 710, and 728.
(The "17" refers to the isolate identification.)

Dapsone synergy with trimethoprim is observed at all ratios with dapsone MIC values decreasing with increasing trimethoprim concentration.

A 20:1 dapsone/trimethoprim combination is selected for more extensive testing with selected strains of the 22 clinical isolates of *Propionibacterium* species previously identified as resistant to dapsone.

Results:
The addition of small amounts of trimethoprim to dapsone results in synergism of "anti-*Propionibacterium*" activity. The Applicant attributes this to the mode of action of trimethoprim acting as a second metabolic blocker in folate production.

For example, the dapsone MIC of *Propionibacterium acnes* ATCC 6919 decreased from 2 to 8 when tested alone to 0.25 to 0.5 µg/mL in a 20:1 combination with trimethoprim, respectively. This represents a 4- to 16-fold improvement in efficacy or a fractional inhibitory concentration (FIC) index of 0.10 to 0.31, thus indicating synergism.

The fractional inhibitory concentration (FIC) index of 0.10 to 0.31 indicates synergism (defined < 0.5 for synergy, 1.0 for additivity, and > 4 as antagonism).

Also, the 20:1 dapsone/trimethoprim is tested against clinical isolates of *Propionibacterium acnes* and *Propionibacterium* species previously resistant to dapsone. Improvements in the dapsone MIC is 8- to 64-fold resistant isolates (i.e., ≥ 32 µg/mL) when tested with dapsone alone. MICs

values in the resistant isolates dropped from ≥ 32 µg/mL to 0.5 to 1.0 µg/mL. The FIC index for the isolates is ≤ 0.05 to 0.19 (= synergism)

The fractional inhibitory concentration (FIC) index for all isolates is ≤ 0.5 to 0.10, indicating synergism. The Applicant explains that the synergism is probably due to the mode of action of trimethoprim acting as a secondary metabolic blocker in folate production.

MICROBIOLOGY STUDY / REPORT RESULTS and DISCUSSION

"Study Synopsis: Study DAP9907 A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and Vehicle Control in Normal Subjects". Study Number: DAP 9907.
Study Title: "A 10-Week, Single-Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and Vehicle Control in Normal Subjects"

From a Microbiological perspective, it is difficult to make any definitive conclusions between the 5% DTG dapsone gel and the Vehicle Control test groups on the exploratory study results in the reduction of the *Propionibacterium* bacterial counts in healthy patients..

The percentage reduction of the *Propionibacterium* bacterial overlap over each other. The 5% DTG formulation reduces the *Propionibacterium* bacterial counts from Baseline 63% to 70% and The Vehicle Control reduces the *Propionibacterium* bacterial counts by 54% to 78%.

The Applicants explains that the failure to detect a difference between 5% DTG and Vehicle Control groups may be due to the small sample size and/or the higher *Propionibacterium* bacterial counts in patients randomized to the Vehicle Control group at Baseline.

The commercial or marketed Dapsone Gel %5 is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily." In this exploratory evaluation study, the gel is applied only to the forehead.

NOTE: The commercial or marketed Dapsone Gel %5 is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily." In this exploratory evaluation study, the gel is applied only to the forehead.

In Vitro SUSCEPTIBILITY
(eNDA 21-794, Document 2692057, Module 2.7.6, 5% DAPSONE TOPICAL GEL, MODULE 2.7.6.18, SYNOPSES OF INDIVIDUAL STUDIES, 040805.pdf, page 79)

"Study Synopsis: 51201 Summary of Reports 51197, 51198, 51199, and 51200: Antimicrobial Susceptibility of *Propionibacterium Acnes* to Dapsone"

Study Number: 51202 (Summary Reports: 51197, 51198, 51199, and 51200, respectively.)
Purpose:
Susceptibility testing of dapsone against *Propionibacterium acnes* and other anaerobic and aerobic bacteria is conducted to evaluate its potential antimicrobial activity in the treatment of acne.

In a non-clinical program for dapsone, the *in vitro* antimicrobial activity of dapsone and other antimicrobials is evaluated against American Type Culture Collection (ATCC) reference stains of the anaerobic bacteria *Propionibacterium acnes*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Eubacterium lentum*, and aerobic bacteria *Staphylococcus aureus* and *Escherichia coli* by minimum inhibitory concentration (MIC) testing. In addition to the reference stains of *Propionibacterium acnes*, clinical isolates of *Propionibacterium acnes* are also tested.
Conclusions:
Dapsone has some activity (i.e., MIC Range = 4 to 16 µg/mL) against *Propionibacterium acnes* and *Propionibacterium* species. However, the effectiveness of dapsone in treating acne vulgaris due to the

aforementioned microorganisms (i.e., essentially *Propionibacterium acnes*) has not been established in adequate and well-controlled trials.

The Applicant's expects the topical application of dapsone to the affected skin will result in locally high concentrations of dapsone; many-fold higher than the MIC_{90} found in this study. The Dapsone Gel 5% is designed to maintain high level dapsone concentrations in the outer layers of the stratum corneum and in the opening of the follicle (pilosebaceous canal) in which *Propionibacterium* species and *Propionibacterium acnes* may reside. The higher concentration of dapsone is expected by the Applicant to contribute to the efficacy of the drug in the treatment of acne.

However, the microbiology susceptibility results and conclusions are problematic. This Spiral Gradient Endpoint-minimum inhibitory concentration (SGE-MIC) procedure is not recognized by the Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards (NCCLS) organization.

APPEARS THIS WAY
ON ORIGINAL

VI. Package Insert Labeling
"Draft" NDA 21-794

ACZONE™ GEL 5% PACKAGE INSERT
(Package Insert Dated: 02.05.05 / F. H. Cross, Jr. (HFD-540) EM Dated: 05/27/05)

NOTE TO READER:

Clinical Microbiology Reviewer's Comments:

-- Deletion = strikeout and shaded yellow (i.e., shaded light): e.g., ~~ACZONE~~

-- Revisions and Comments = shaded yellow (i.e., shaded light): e.g., ~~ACZONE~~ now written as dapsone.

Applicant's Comments:

-- Deletions = strikeout and shaded black (i.e., shaded dark): e.g., ~~*Antibacterial.*~~

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 1

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

cc: Orig. NDA 21-794
HFD-540/Div.Dir./J.Wilkin
HFD-540/Dep.Div.Dr./S.Kukich
HFD-540/TLMO/M.Luke
HFD-540/MO/B.Vaugh
HFD-540/ProjMgr/F.Cross,Jr.
HFD-520/ClinMicroRew/H.V.Silver
Filename: N21794-HVS-FIN
LABELING APPROVAL

Concurrence Only:
FMarsik/TL Micro/HFD-520 Finalized 6/21/05 FJM

HFD-520/DepDivDir/L.Gavrilovich

BIBLIOGRAPHY

[1] Plewig G. and A.M. Kligman. Acne and Rosacea. Springer-Verlag. New York. 1993.

[2] Harper J.C. and D. Thiboutot. Pathogenesis of Acne: Recent Research Advances. Adv. Dermatol. 2003;19:1-10.

[3] Jape U. Pathological Mechanisms of Acne with Special Emphasis on *Propionibacterium acnes* and Related Therapy. Acta. Derm. Venereol. 2003; 83:241-248.

[4] Mandell G.L. and M.A. Sande. Antimicrobial Agents. Gilman A.G., Rall T.W., Nies A.S., and P. Taylor, Eds. The Pharmacological Basis of Therapeutics. Eighth Edition. New York: Pergamon Press. 1990;1048.

[5] Wozel G. and J. Barth. Current Aspects of Modes of Action of Dapsone. Intl. J. Derm. 1988;27(8):547-552.

[6] Data on File at Atrix Laboratories. Laboratory Notebook: KG1064-18.

[7] Jeremy A.H., Holland D.B., Roberts S.G., Thomson K.F. and W.J. Cunliffe. Inflammatory Events are involved in Acne Lesion Initiation. J. Invest. Dermatol. 2003;121(1):20-27.

[8] Paniker U. and N. Levine. Dapsone and Sulfapyridine. Dermtol. Clin. 2001;19(1):79-86.

[9] Kazmierowski J.A., Ross J.E., Peizner D.S., and K.D. Wuepper. Dermatitis herpetiformis: effects of sulfones and sulfonamides on neutrophil myeloperoxidase-mediated iodination and cytotoxicity. J. Clin. Immunol. 1984;4(1):55-64.

[10] Maloff B.L., Fox D., Burin E., and T.M. Di Meo. Dapsone Inhibits LTB_4 Binding and Bio-response at the Cellular and Physiologic Levels. Eur. J. Pharmacol. 1988;158(1-2):85-89.

[11] Debol S.M., Herron M.J., and R.D. Nelson. Anti-inflammatory Action of Dapsone: Inhibition of Neutrophil Adherence is Associated with the Inhibition of Chemoattractant-induced Signal Transduction. J. Leukoc. Biol. 1997;62(6):827-836.

[12] Coleman M.D. Dapsone: Modes of Action, Toxicity and Possible Strategies for Increasing Patient Tolerance. Br. J. Dermatol. 1993;129:507-513.

[13] Matsuoka, M. A. Dec 2000. *Mycobacterium leprae* isolate resistant to dapsone, rifampin, ofloxacin and sparfloxacin. Int J Lepr Other Mycobact Dis. 68(4):452-5.

[14] MICROBIOLOGY REPORT 51200: Improvement of Dapsone MIC by Synergism with Trimethoprim. Appendix 3 Micro. Report 51200: Module 5, Vol. 117. August 25, 2004.

[15] Hill G.G. Spiral Gradient Endpoint Method Compared to Standard Agar Dilution for Susceptibility Testing of Anaerobic Gram-Negative Bacilli. Journal of Clinical Microbiology. May 1991; Vol.29(5):975-979

[16] Lorian V. Antibiotics in Laboratory Medicine. Williams & Wilkins, Baltimore, MD. Fourth Edition. 1996;17:824-825.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Harold Silver
6/23/05 03:35:27 PM
MICROBIOLOGIST

Please sign off on the Clinical Microbiology Review on NDA 21-794, ACZONE (dapsone) Gel 5%, for the topical treatment of acne vulgaris.

Frederic Marsik
6/28/05 ~~0~~6:24:08 AM
MICROBIOLOGIST

Lillian Gavrilovich
6/29/05 03:30:51 PM
MEDICAL OFFICER

Product Quality Microbiology Review
Review for HFD-540

11 MARCH 2005

NDA: 21-794

Drug Product Name
Proprietary: ACZONE 5%
Non-proprietary: dapsone topical gel
Drug Product Priority Classification: S

Review Number: 1

Subject of this Review
Submission Date: 31 August 2004
Receipt Date: 7 September 2004
Consult Date: 6 October 2004
Date Assigned for Review: 7 October 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Atrix Laboratories, Inc.
Address: 2579 Midpoint Drive, Ft Collins, CO 80525
Representative: Lynn Hanson
Telephone: 970-212-4894

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** New NDA (505(b)(2))

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Atrix Laboratories
Fort Collins, CO

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Non-sterile, preserved, topical gel, 3 or 30 g/tube

5. **METHOD(S) OF STERILIZATION:** N/A

6. **PHARMACOLOGICAL CATEGORY:** Treatment for acne vulgaris

B. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** N/A

filename: N021794R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a non-sterile, preserved topical gel.

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
David Hussong, Ph.D. (Microbiology Supervisor)

C. CC Block
N/A

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bryan Riley
3/14/05 10:59:03 AM
MICROBIOLOGIST

David Hussong
3/14/05 12:19:07 PM
MICROBIOLOGIST