CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 019931

Trade Name : KLARON LOTION 10%

Generic Name: Sodium Sulfacetamide Lotion 10%

Sponsor : Dermick Laboratories, Inc.

Approval Date: December 23, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-931

Dermik Laboratories, Inc.
Attention: Ronald F. Panner
Group Director, Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426

DEC 23 1996

Dear Mr. Panner:

Reference is made to your new drug application (NDA) dated December 22, 1988, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Klaron (sodium sulfacetamide lotion) Lotion, 10%, formerly identified as Sulfacet Clear Lotion, 10%.

Reference is also made to the not approvable letters dated September 28, 1989, and October 30, 1990, and to the approvable letter dated June 19, 1996. We acknowledge receipt of your additional communications dated June 18, July 3, August 23 and 26, and October 25, 1996.

This new drug application provides for the treatment of acne vulgaris.

We have completed the review of this application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed, revised, draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. The enclosed, revised, draft labeling and carton labels were stated to be acceptable in your facsimile dated December 23, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

We also acknowledge receipt of your facsimile dated December 6, 1996, in which you have committed to revise the container label to be consistent with the enclosed, revised, draft labeling. You have committed to implement these changes in the container and carton labels at the next printing.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after is is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 19-931. Approval of this submission by FDA is not required before the labeling is used.

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

We remind you of your Phase 4 commitment specified in your submission dated July 3, 1996. This commitment is listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplement, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitments."

We also acknowledge your commitment of July 3, 1996, to conduct accelerated-condition stability as well as labeled storage condition studies on the first three full-scale commercial production lots.

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

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

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

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

If you have any question, please contact:

Kevin Darryl White, M.B.A.
Project Manager
(301) 827-2023

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ENCLOSURE

The reviewers of this application were:

Ella Toombs, M.D., Medical Officer, HFD-540
Janet Higgins, Chemist, HFD-540
Syed N. Alam, Ph.D., Pharmacologist/Toxicologist, HFD-540
Ralph Harkins, Ph.D., Biostatistician, HFD-725
E. Dennis Bashaw, Pharm.D., Biopharmaceutist, HFD-880
Kevin Darryl White, M.B.A., Project Manager, HFD-540

cc:
Original NDA 19-931
HFD-540/Div. files
HFD-540/PROJ MGR/White/12.04.96
HFD-540/ACTING SUPV PROJ MGR/Kozma-Fornaro/12.04.96
HFD-540/MO/Toombs
HFD-540/DIV DIR/Wilkin
HFD-540/CHEM/Higgins
HFD-540/CHEM TL/DeCamp
HFD-540/PHARM/Alam
HFD-540/PHARM TL/Jacobs
HFD-725/BIOSTAT TL/Srinivasan
HFD-880/BIOPHARM TL/Bashaw
HFD-520/MICRO/Creedon
HFD-520/MICRO TL/Sheldon
HFD-2/M.Lumpkin
HFD-105/M.Weintraub
HFD-830/E.Sheinin
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735 (with labeling)

drafted: KDW/December 4, 1996/NDA 19-931
r/d Initials:
final:

APPROVAL
PHASE 4 COMMITMENT

DHL

NDA 19-931

JUN 19 1996

Dermik Laboratories, Inc.
Attn: Ronald F. Panner
Group Director, Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426

Dear Mr. Panner:

Reference is made to your new drug application (NDA) dated December 22, 1988, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulfacet Clear (sodium sulfacetamide lotion) Lotion, 10%.

Reference is also made to the not approvable letters dated September 28, 1989, and October 30, 1990. We acknowledge receipt of your additional communications dated November 8, 1990; January 25 (two identical), March 22, April 9, and October 15, 1991; March 4, May 12 and 13, June 24, July 1 and 21, and September 9 and 23, 1994; January 30, February 27, March 10, and December 12, 1995; and February 21 and 22, and March 12, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following:

1. Revised draft labeling for the drug product that is identical to the enclosed draft labeling. Should additional information relating to the safety or effectiveness of this drug product become available, further revision of the labeling may be required.

2. Under 21 CFR 314.50 (d) (5) (vi) (b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

   A. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs. now will certainly facilitate review.

   B. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

   C. Provide details of any significant changes or finding, if any.

   D. Summarize worldwide experience on the safety of this drug.

E. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

3. A commitment to conduct the following as a Phase IV request:

4. As a result of the unsatifactory current good manufacturing practices (cGMP) inspections dated May 1, 1995 to June 23, 1995 the following requests are listed below:

   A. An updated manufacturing procedure describing the equipment to be used and the mixing/holding times.

   B. New accelerated-condition stability data from recently manufactured lots and a commitment to conduct labeled storage condition studies on the first three full-scale commercial production lots.

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (cGMP) is required before this application may be approved.

In addition, although not the basis for the approvability of this application, the standard operating procedure (SOP) for the microbial limits test should be provided.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

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

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

In accordance with the policy described in 21 CFR 314.102 (d) of the new drug regulations, you may request an informal conference with the members of the Division of Dermatologic and Dental Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting should be requested at least 15 days in advance.

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

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

Should you have any questions concerning this application, please contact:

Kevin Darryl White, M.B.A.
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

6/14/96

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

cc:
Orig NDA19-931
HFD-2/Lumpkin
District Office-PHL
HFD-105
HFD-80
HFA-100
HFC-130
HFD-5
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/MO/Toombs/04/08/96
HFD-540/PHARM/Alam/04/08/96
HFD-540/CHEM/Higgins/04/16/96
HFD-520/MICRO SUPV/Sheldon/04/15/96
HFD-426/BIOPHARM/Ajayi/04/09/96
HFD-725/BIOSTAT/Srinivasan/04/09/96
HFD-725/BIOSTAT/Harkins/04/09/96
HFD-40/DDMAC/Raymond
HFD-540/PROJ MGR/White/04/05/96

Concurrence only:
HFD-540/DEP DIR/Katz/04/17/96
HFD-540/PHARM SUPV/Jacobs/04/16/96
HFD-540/CHEM SUPV/DeCamp/04/16/96
HFD-540/PROJ MGR SUPV/Cook/04/16/96

APPROVABLE
PHASE IV COMMITMENT

NDA 19-931

Mr. Ronald F. Panner
Director, Regulatory Affairs
Dermik Laboratories, Inc.
500 Virginia Drive
Fort Washington, Pennsylvania 19034

OCT 30 1990

Dear Mr. Panner:

Reference is made to your New Drug Application (NDA) dated December 22, 1988, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulfacet Clear (sodium sulfacetamide) Lotion, 10%.

Reference is also made to the not approvable letter dated September 28, 1989. We acknowledge receipt of your additional communications dated October 25, 1989 and June 26, 1990.

We have completed the review of this application, as amended, and have concluded that the information presented is inadequate and that the application is not approvable.

Under section 505(d) of the Act and 21 CFR 314.125(b) of the FDA implementing regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Sulfacet Clear (sodium sulfacetamide) Lotion, 10%, will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, each clinical study did not include an acceptable physician global evaluation.

The testimonials from the clinical investigators, which were included in the submission dated June 26, 1990, were inadequate. The testimonials included statements by the clinical investigators that the improvement observed by the patients in the clinical studies was clinically significant. However, they do not provide an evaluation of the progress of each patient. A physician global evaluation would be expected to analyze the progress of each patient from baseline disease status at each evaluation visit. It is recommended that the progress be measured on a graduated scale. Such a scale may be comprised, for example, of five numbered gradations of improvement from "0" (no change or exacerbation) to "4" (disease cleared).

Please be advised that the information submitted in response to the chemistry, manufacturing, and controls deficiencies specified in

the not approvable letter dated September 28, 1989 was evaluated and found to be acceptable.

We reserve comment on the proposed labeling until the New Drug Application is found adequate in other aspects.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of an intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial response will not be processed as a major amendment, and, therefore, the review clock will not be activated.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA 19-931
PHI-DO
HFD-82
HFD-500
HFD-520
HFD-520/DIV DIR/Lumpkin
HFD-520/MO/Bostwick MML 10-30-90
HFD-520/MO SUPV/Chambers
HFD-520/PHARM SUPV/Osterberg
HFD-520/CHEM/Shetty
HFD-520/CHEM SUPV/De Camp
HFD-521/PROJ MGR/Cook

NOT APPROVABLE

10-30-90

MML 10/30/90

NDA 19-931

Mr. Ronald F. Panner
Dermik Laboratories, Inc.
Fort Washington, Pennsylvania 19034

Dear Mr. Panner:

Reference is made to your New Drug Application (NDA) dated December 22, 1988, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Sulfacet (sodium sulfacetamide) Lotion, 10%.

We have completed our review and conclude that the information presented is inadequate and that the application is not approvable. Under section 505(b)(1) of the Act and 21 CFR 314.125(b) of the regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies to assure that this product will have the effect it is represented to have under the conditions of use recommended in the labeling. Specifically, the clinical studies failed to include a global evaluation by the physician.

We do not consider the patient global evaluation results to be reliable because of the subjective nature of patient reaction to therapy. Since the results of the inflammatory lesion counts indicate that the active product is only marginally superior to the placebo, the physician global evaluation becomes even more important to the overall interpretation of the study.

The manufacturing control information submitted in support of this application is inadequate as follows:

1. The quantitative composition of the drug product should be stated in percentages based on volume, since the drug product is a liquid. The batch composition for manufacturing purposes may be stated in terms of weights, since this reflects normal manufacturing practice, but any such statement should be accompanied by a density or equivalent volume for purposes of comparison, unless density or specific gravity is a specification for the ingredient. In addition, a measured density for the formulation should be provided to permit conversion of w/w percentages to w/v percentages.

2. The individual ingredients identified as
must be identified by trade name, as well as chemical name, and the composition stated.

3. The specifications associated with test method
are not assays, but limits on reacted precursors. An assay method which is specific for the ingredient purported to be present must be submitted.

4. The specifications for microbial limits should identify the other specifies which are regarded as

5. Drug Master File (DMF) reference should be supplied for

6. Suppliers of non-compendial inactive ingredients must be identified by name and address, and the specific product to be used identified.

7. The batch manufacturing instructions should be revised to provide for adjustment of the amount of sulfacetamide sodium by the results of the water analysis.

8. The target strength for the formulation must be 100% of label claim.

9. The laboratory controls used to assure the identity, strength, quality and purity of the drug product are inadequate to control the finished drug product as follows:

   A. The pH specification must state whether the measurement is to be made on neat or diluted drug product.

   B. A description of lot control numbering which is capable of yielding the complete manufacturing history of the package has not been submitted.

   C. In addition, consideration should be given to using the published assay method for sulfacetamide sodium (USP XXI, Supp. 7, pg. 2834).

10. The stability data reported are inadequate to support the proposed expiration date of twenty-four months for the drug product as follows:

    A. The dates of manufacture are not stated.

    B. No lot includes reports of measurements beyond twelve months.

11. Testing at the three month testing station must be included in future stability studies, as described in the stability protocol.

12. The labels and labeling are inadequate to insure the safe and effective use of the drug as follows:

    A. The abbreviation should be used instead of for in the final printed labeling.

    B. is not the same as the NF name must be used.

13. Typographical errors in the right panels of the container label and carton must be corrected as follows:

A. should have a space following

B. Methyl paraben is misspelled (on the label only).

14. We recommend that the stability protocol be revised as follows:

A. pH should be included among the specifications to be tested.

B. Any reworked lot should be placed on stability study.

C. Results of the ongoing stability studies should be reported each year in the annual report, rather than only upon extension of the shelf life or withdrawal of a lot from the market.

15. We wish to bring to your attention that the compendial monograph referenced in your application for the control of permits the use of sodium metabisulfite Since no monograph for appears in USP XXI/NF XVI, we recommend that you consider the identity of the material you propose to use in the formulation, and, if appropriate, make the following revisions:

A. Replace as an ingredient with

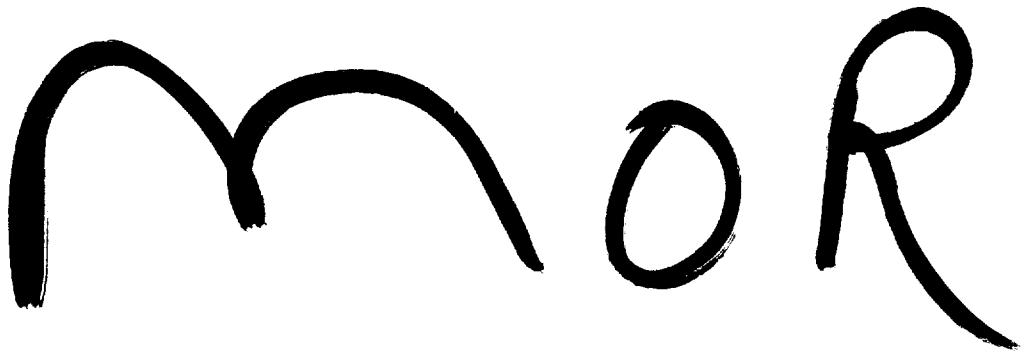
B. Make corresponding changes in the draft labels and labeling.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the Food and Drug Administration may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial reply will not be processed as a major amendment unless it addresses all remaining outstanding deficiences, nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely yours,

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA
HFD-82/HFD-710
HFD-220/HFD-500
HFD-520/HFD-520/LGavrilovich
HFD-520/CCEvans/HFD-520/WHDeCamp
HFD-520/JMDavitt/HFD-520/ARCasola
HFD-520/ROsterberg
HFD-520/DCBostwick:elp/09/26/89
5111m


mor

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 19-931 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: KLARON LOTION (SODIUM SULFACETAMIDE LOTION, 10%) Action: (AP) AE NA

Applicant DERMIK LABORATORIES Therapeutic Class 35

Indication(s) previously approved NOT PREVIOUSLY APPROVED

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___ N/A

Indication in this application ACNE VULGARIS

(For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required. PREGNANCY CATEGORY C * STE IN PEDIATRIC PATIENTS UNDER 12 HAS NOT BEEN ESTABLISHED.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

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

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

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

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

OK

X 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form. Safety and efficacy not established <12 yr. PG Category C.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[signature] 11/29/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 19-931
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

[signature] - 12/21/96

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

5/95

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 19-931 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Sulfacet Clear (Sodium Sulfacetamide) lotion, 10% Action: AP AE (NA)

Applicant Dermik Laboratories Therapeutic Class 35

Indication(s) previously approved Not previously approved

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___ N/A

Indication in this application Acne vulgaris

(For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required. Pregnancy Category C. Safe in pediatric patients under 13 has not been established.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

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

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

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

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[signature] PM — 12/14/95

Signature of Preparer and Title (PM, CSO, MO, other) — Date

6/13/96

cc: Orig NDA/PLA # 19-931
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

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

5/95

N.B. Discussed with D. Tuab on 12/14/95.

DEC 2 1994

Medical Officer's Review of NDA 19-931

	Submission Date:	March 4, 1994
	Review Date:	November 28, 1994
Sponsor:	Dermik Laboratories 500 Arcola Road Collegeville, PA 19426	
Product Name:	Generic - Sodium Sulfacetamide 10% Trade - Sulfacet Clear Lotion	
Pharmacological Class:	Topical antibiotic	
Proposed Indication:	Acne vulgaris	
Route of Administration:	Topical	
Proposed Dosage:	Twice daily	
Related NDAs:	NDA 5-963	Sulfacetamide 10-30% Ophthalmic Solution and Ointment
	NDA 10-210, 12-813, 18-988	Sulfacetamide / Steroid Combination Products
Related Reviews:	MOR dated 8/19/94 MOR dated 9/10/94 Statistical Review dated 7/29/94	

Reviewer Comment:

This NDA was originally submitted on December 22, 1988 and received a "not approvable" letter dated September 28, 1989, on the basis that the studies failed to include a physician's global evaluation as part of the efficacy criteria (See Clinical Review dated August 19, 1989). The applicant responded with the submission of two "testimonial letters" supporting the efficacy of the product. A second, "not approvable" letter was issued repeating the requirement for a physician's global evaluation. (See Clinical Review dated September 10, 1990). The current submission consists of two completed clinical studies.

This product has been widely used by dermatologists for many years.

Protocol DL-6013-9102(01) **A Controlled, Double-Blind Study Comparing Sodium Sulfacetamide Solution and Vehicle**

Principal Investigator: Lawrence C. Parish
1819 John F. Kennedy Blvd
Philadelphia, Pennsylvania 19103

Investigational Review Board: Exxex Institutional Review Board
60F Apgar Way
Lebanon, New Jersey 08833

Study Design: This was a double-blind, single center, randomized, vehicle controlled study designed to assess the efficacy and safety of topically applied sodium sulfacetamide 10% lotion in the treatment of acne vulgaris.

Number of Subjects: 70

Ages of Subjects: 13 years to 30 years

Demographics:

Gender -	31 Males	39 Females
Race -	30 Caucasians	28 Blacks
	4 Orientals	4 Hispanics
	3 American Indians	1 Arabic

Inclusion Criteria:

- Grade II - III acne
- 20 to 60 inflammatory lesions
- 20 to 100 comedones

Exclusion Criteria:

- Known hypersensitivity to sulfur or related compounds
- Patients who are pregnant for lactating
- Treatment with systemic antibiotics within 4 weeks of study enrollment
- Treatment with topical antibiotics within 2 weeks of study enrollment

Study Plan: Patients who met the clinical designation of Grade II or Grade III, mild to moderate acne, having a range of 10 to 80 facial comedones and 20 to 80 inflammatory were enrolled and instructed to apply the topical preparation to the facial skin twice daily. Efficacy variables which were used to assess patient response to treatment included a reduction from baseline in the number of comedones, papules/pustules and acne grade. These variables in addition to physician and patient overall assessment were monitored at weeks 2, 4, 6, 8 and 10.

Reviewer's Comments:

The parameters and evaluation points chosen by the sponsor in order to assess efficacy of the drug product were appropriate. There were no references to safety evaluations included in the study design, however adverse events were recorded and the results are included at the end of the study tabulation.

End of Study Tabulation Results by Treatment Group

	Sodium Sulfacetamide	Vehicle
	(number of subjects)	(number of subjects)
Disposition		
Enrolled	35	35
Completed	20	18
Discontinuations	15	17
Voluntarily Left	5	5
Missed 2 Visits	7	5
Lack of Efficacy	3	2
Lost to Follow-up	0	2
Adverse Reactions	0	3

Reviewer's Comments: *The percentage of completed subjects is relatively low in each group.*

Count Inflammatory Lesions

	Sodium Sulfacetamide			Vehicle		
	n	mean	percent reduction from baseline	n	mean	percent reduction from baseline
Baseline	32	22.6		30	26.5	
2 Weeks	30	17.8	18%	25	24.3	6%
4 Weeks	27	17.4	23%	24	25.1	12%
6 Weeks	21	13.5	39%	20	26.9	<1%
8 Weeks	17	12.6	49%	17	19.6	30%
10 Weeks	20	11.6	50%	18	30.2	-1%

p value for reduction from baseline = 0.002
p value for percent reduction = 0.001

Count Comedones

	Sodium Sulfacetamide			Vehicle		
	n	mean	percent reduction from baseline	n	mean	percent reduction from baseline
Baseline	32	36.1		30	33.7	
2 Weeks	30	27.8	20%	25	27.9	16%
4 Weeks	27	27.1	28%	24	24.1	30%
6 Weeks	21	22.5	34%	20	29.8	10%
8 Weeks	17	18.2	47%	17	27.2	21%
10 Weeks	20	17.8	49%	18	34.1	4%

p value for reduction from baseline = 0.021
p value for % reduction from baseline = 0.005

Acne Grade	Sodium Sulfacetamide I /II /III /IV	Vehicle I /II /III /IV	p-value
Baseline	0 10 22 0	0 8 22 0	.69
2 Weeks	0 5 25 0	0 7 18 0	.17
4 Weeks	0 4 23 0	0 3 19 1	.65
6 Weeks	1 3 17 0	0 2 16 1	.28
8 Weeks	2 4 11 0	0 1 16 0	.07
10 Weeks	5 1 14 0	0 0 18 0	.02

Physician's Assessment	Sodium Sulfacetamide	Vehicle
Worse	4 (16.7%)	5 (20.8%)
No Change	1 (4.2%)	9 (37.5%)
Slight Improvement*	2 (8.3%)	3 (12.5%)
Moderate Improvement	8 (33.3%)	6 (25.0%)
Excellent Improvement	9 (37.5%)	1 (4.2%)

p value = 0.005

Patient's Assessment	Sodium Sulfacetamide	Vehicle
Worse	4 (15.4%)	6 (23.1%)
No Change	3 (11.5%)	7 (26.9%)
Slight Improvement	4 (15.4%)	6 (23.1%)
Moderate Improvement	8 (30.8%)	5 (19.2%)
Excellent Improvement	7 (26.9%)	2 (7.7%)

p value = 0.037

	Sodium Sulfacetamide	Vehicle
Patient's Comparison with Previous Treatment		
Worse	1 (4.0%)	4 (14.3%)
No Difference	1 (4.0%)	5 (17.9%)
Slightly Better	4 (16.0%)	6 (21.4%)
Much Better	5 (20.0%)	3 (10.7%)
Not Applicable	14 (56.0%)	10 (35.7%)

p value = 0.07

Reviewer's Comments:

All of the values provided are those submitted by the sponsor; the results were confirmed by the agency statistician. The submission is the applicants response to the agency's request for a physician's global evaluation, the results of that evaluation demonstrate statistical significance favoring sulfacetamide. The inclusion of the patients' comparison to previous treatment is not supportive of the sponsors' claim.

Adverse Events (AE)

Study DL-6013-9102 (Dr. Parish)

	Sodium Sulfacetamide (35 patients each group)		**Vehicle** (35 patients each group)	
	N	(%)	N	(%)
All Patients (70):				
Had at least one AE	2	6%	5*	14%
Had a drug-related AE	0	0	2	6%
Discontinued because of AE	0	0	3*	9%
Discontinued because of drug-related AE	0	0	2	6%

Adverse Event	Group	N	(%)	severity
increased acne	Sulfacetamide	1	2.9	mild
itching	Sulfacetamide	1	2.9	mild
soreness,itching, redness*	Vehicle	1	2.9	moderate
urticaria*	Vehicle	1	2.9	mild
redness and scaling on left flank (pityriasis rosacea)	Vehicle	1	2.9	mild
pain, left shoulder due to auto accident)	Vehicle	1	2.9	mild

* indicates patient discontinued due to AE - Although Patient #69 in the vehicle treatment group did not have an AE listed on his AE FORM, the reason for discontinuation was listed as due to adverse experience (worsening acne).

Protocol DL-6013-9302	**A Controlled, Double-Blind Study Comparing Sodium Sulfacetamide and Vehicle**
Principal Investigators:	J. Michael Moloney, MD 3535 Cherry Creek North Drive Denver, Colorado 80290 Richard S. Berger, MD Hill Top Research, Inc. 223 Route 18, Suite 203 East Brunswick, New Jersey 08816
Investigational Review Board:	Summit Institutional Review Board 1630 30th Street, Suite 488 Hill Top Research Miamiville, Ohio 45147
Study Design:	This was a double-blind, multi-center, vehicle controlled study designed in order to assess the efficacy of sodium sulfacetamide 10% solution when compared to vehicle in the treatment of patients with mild to moderately severe acne vulgaris.
Number of Subjects:	140
Ages of Subjects:	13 years to 30 years

Demographics:	Male	70	Female	70
Race:	Caucasian	127	Black	7
	Hispanic	4	Oriental	3
	Asian	2	Other	7

Inclusion Criteria:	The same as in the previously described study except: subjects were to have at least 10 and no more than 60 inflammatory lesions and or 20 but no more than 100 comedones.
Exclusion Criteria:	Identical to the previously described study.

Study Plan: Patients were randomized to one of two treatment groups (sodium sulfacetamide or vehicle) and instructed to apply the study drug twice daily for the ten week study duration. Evaluations were made at baseline, and weeks 2, 4, 6, 8 and 10 in order to assess changes in the comedonal and inflammatory lesion counts, physicians and patients global assessments as in the previously described study. Note: patient assessment of comparison to previous treatment was not evaluated in this study.

Reviewer's Comments: *This study shared the plan of the previously described study with the exception as noted and is appropriately designed to answer the agency concerns.*

Tabulation of Results by Treatment Group

	Sodium Sulfacetamide	Vehicle
	Number of Subjects	Number of Subjects
Enrolled	70	70
Completed	63	58
Discontinuations	7	12
Voluntarily left study	3	8
Protocol violation	3	1
Adverse reaction	1	1
Loss to follow-up	0	2

Count Inflammatory Lesions

	Sodium Sulfacetamide			Vehicle		
	n	mean	percent reduction from baseline	n	mean	percent reduction from baseline
Baseline	67	23.4		68	22.4	
2 Weeks	67	16.9	24%	68	18.9	17%
4 Weeks	65	13.5	39%	66	15.5	31%
6 Weeks	63	11.1	50%	61	12.9	44%
8 Weeks	62	9.6	57%	58	12.3	46%
10 Weeks	63	8.7	61%	58	10.9	52%

p value for reduction from baseline = .20
p value for % reduction from baseline = .02

Count Comedones

	Sodium Sulfacetamide			Vehicle		
	n	mean	percent reduction from baseline	n	mean	percent reduction from baseline
Baseline	67	38.5		68	37.2	
2 Weeks	67	36.7	5%	69	34.1	8%
4 Weeks	65	34.3	10%	66	33.0	20%
6 Weeks	63	32.4	17%	61	31.2	16%
8 Weeks	62	32.3	16%	58	32.4	11%
10 Weeks	63	32.6	16%	58	31.7	18%

p value for reduction from baseline = .55
p value for % reduction from baseline = .77

Physician's Assessment
Improvement from Baseline

	Sodium Sulfacetamide		Vehicle		
	n	score	n	score	p-value
2 Weeks	67	9.4	68	9.9	.72
4 Weeks	65	21.6	66	17.4	.05
6 Weeks	63	31.2	61	27.2	.25
8 Weeks	62	39.1	58	33.4	.02
10 Weeks	63	46.0	58	38.5	.01

	Sodium Sulfacetamide		Vehicle	
Patient's Assessment				
Worse	0	0%	2	3%
No Change	4	6%	3	5%
Slight Improvement	16	25%	12	20%
Mild Improvement	17	27%	21	35%
Moderate Improvement	15	23%	21	35%
Excellent Improvement	12	19%	1	2%

p value = 0.23

Reviewer's Comments:

The results of this study demonstrate a clinically significant reduction in the percent of inflammatory lesions and improvement from baseline in the physicians global assessments in the sodium sulfacetamide vs vehicle treated group. The assessment of comedones did not illustrate the same degree of improvement in the second study, however, when comparing the overall results in both studies there is a clear advantage favoring sodium sulfacetamide.

Adverse Events (AEs) Study DL6013-9302 (Dr. Berger and Dr. Maloney)

	Sodium Sulfacetamide (70 patients)		Vehicle (70 patients)	
	N	(%)	N	(%)
All Patients (140):				
Had at least one AE	13	19	9	13
Had a drug-related AE	1	1	3	4
Discontinued because of AE	1	1	1	1
Discontinued because of drug-related AE	1	1	0	0

Adverse Event	Group	N	(%)	severity
erythema, edema and itching (due to sunburn)*	Sulfacetamide	1	1.4	moderate
cystic acne lesion (right lower lid)	Sulfacetamide	1	1.4	moderate
dislocated shoulder *	Sulfacetamide	1	1.4	moderate
yeast infection (vaginal)	Sulfacetamide	1	1.4	mild
rectal polyp (removal)	Sulfacetamide	1	1.4	mild
sunburn	Sulfacetamide	3	4.3	mild (3)
dryness/cracking (mouth)	Sulfacetamide	1	1.4	mild
diarrhea	Sulfacetamide	1	1.4	mild
pneumonia	Sulfacetamide	1	1.4	mild
asthma	Sulfacetamide	1	1.4	mild
fracture (right index finger)	Sulfacetamide	1	1.4	moderate
strep throat	Sulfacetamide	1	1.4	moderate
chapping	Vehicle	1	1.4	mild
burning/stinging	Vehicle	2	2.9	mild (2)
dry and flaky	Vehicle	1	1.4	mild
pink eye	Vehicle	1	1.4	mild
poison Ivy (face and arms)*	Vehicle	1	1.4	moderate
sunburn	Vehicle	2	2.9	mild/moderate
pruritus (secondary to UVA exposure)	Vehicle	1	1.4	moderate
antibiotic use (patient refused to divulge indication)	Vehicle	1	1.4	mild

* indicates patient discontinues due to AE

Reviewer's Comments: *The incidence of adverse was minimal in both groups, in both studies. The studies submitted support the safety of sodium sulfacetamide in the treatment of acne vulgaris.*

4 Pages deleted

Labeling

Revisions

Conclusions:

1. The submitted studies demonstrate statistical superiority of sulfacetamide over vehicle in physician's assessment.

2. The submitted studies in combination with the previously submitted studies support the safety and efficacy of sulfacetamide in the treatment of acne vulgaris.

3. The labeling should be revised as identified in this review.

Recommended Regulatory Action:

NDA 19-931 is recommended for approval with the labeling revisions identified in this review.

Ella L. Toombs, MD

cc: NDA 19-931
HFD-540
HFD-340
HFD-540/Chambers 11/29/94
HFD-540/CSO/Cook
HFD-540/CHEM/Mokhtari-Rejali
HFD-540/PHARM/Alam
HFD-540/MO/Toombs

12/2/94

Date of Review: April 3, 1991

Clinical Review of Amendment to NDA 19-931

Sponsor: Dermik Laboratories, Inc.
Fort Washington, PA

Drug: Sulfacet (sodium sulfacetamide) Clear Lotion, 10%.

Category: Anti-acne product

Date of Submission: March 22, 1991. The original NDA was filed December 22, 1988.

Background:

Please see the previous clinical reviews dated August 18, 1989 and September 10, 1990. This NDA has been made "not approvable" twice because a physician global evaluation was not done when the pivotal clinical studies were performed. The March 22, 1991 submission provides an outline for a clinical study to address this deficiency.

Material Reviewed:

The sponsor proposes to perform a single parallel group comparison of Sulfacet Lotion and its vehicle in the treatment of acne vulgaris. Thirty male and female patients aged 13-30 years are to be studied. They will have Grade II or III acne with a minimum of 10 and a maximum of 100 inflammatory lesions at study entrance. They are to be treated for two weeks. The only efficacy variable to be studied is investigator's global evaluation on a scale from 0 = worse to 4 = excellent improvement.

Recommendation:

The proposed protocol has many deficiencies. The sponsor should be notified of the following comments:

1. Two independent studies are necessary to obtain approval of the NDA.

2. Lesion counts as well as global evaluation should be performed. Inflammatory lesions (papules and pustules) as well as total lesion counts should be done.

3. The number of patients proposed is too small. A minimum of 30 patients per treatment group (preferably more) is necessary to assurestatistical significance of the results.

4. The study should be performed for a period of at least 10 weeks.

5. The number of inflammatory lesions at entrance should be in the range of 20-60. (The proposed range of 10-100 raises the possibility that one or two patients with a high lesion count at entrance could unduly influence the results).

6. The studies should be performed under an IND. Apparently the studies submitted for the original NDA were not part of an IND.

David C. Bostwick

Wiley A. Chambers, M.D.

cc: Orig. NDA 19-931
HFD-520/PHARM/Osterberg
HFD-520/CHEM/Shetty
HFD-520/CSO/RCook
HFD-520/MO SUPV/WChambers
HFD-520/MO/Bostwick

#6 is not a requirement (if studies done outside USA) - Clearly under the IND (USA or non-US) would be preferred. 4/25/91

Date Review Begun: September 10, 1990
Date Review Completed: September 10, 1990

Clinical Review of Amendment to NDA 19-931

Sponsor: Dermik Laboratories, Inc.
Fort Washington, PA 19034

Drug: Sulfacet (sodium sulfacetamide) Clear Lotion, 10%.

Category: This product is intended for the topical treatment of acne vulgaris. It is to be use 1-3 times daily.

Date of Submission: December 22, 1988. The amendment reviewed here is dated June 26, 1990.

Background: In a review completed on August 19, 1989, Mr. Bostwick and Dr. Evans found this application to be not approvable no because physician global evaluation of the progress of the patients was done (the patients rated their own progress). We have not recommended other topical acne products for approval without physician global assessments.

In a letter dated September 28, 1989, the Division made the application not approvable because the physician global evaluation was lacking and because a number of deficiencies were present in the manufacturing control information. The June 20, 1990 amendment replies to the not approvable letter.

Chemistry Review: Since the reviewing chemist was Dr. DeCamp, we assume that a new reviewer will be named. No review of the new chemistry information is available at this time.

Material Reviewed: The sponsor has provided letters from the clinical investigators (Drs. Swinyer and Jurnovoy) which are statements that the improvement seen by the patients in their studies was clinically significant. Those testimonials do not provide the patient-by-patient evaluation of the progress of each test subject from baseline to the end of treatment which we require for physician global analysis. This should be explained to the sponsor.

Conclusion and Recommendation: The sponsor should be informed that the application remains not approvable because an acceptable physician global analysis is not available. Specifically, a physician global analysis would be expected to evaluate the progress of each patient from baseline disease status at each evaluation visit. The progress should be measured on a graduated scale (typically, five numbered gradations of improvement from 0 = no change or exacerbation to 4 = disease cleared).

Two additional clinical studies which include this type of evaluation in the study protocol are necessary for approval of this NDA.

David C. Bostwick

Wiley A. Chambers M.D.
Medical Officer

cc: Orig. NDA
HFD-340
HFD-520
HFD-520/PHARM/ROsterberg
HFD-520/CHEM/WHDeCamp
HFD-520/WAChambers
HFD-520/DCBostwick/llm/9/10/90
N19931.REV

10/1/90

Date Review Begun: July 19, 1989
Date Review Completed: August 19, 1989

Clinical Review of Original NDA 19-931

Sponsor: Dermik Laboratories, Inc.
Fort Washington, PA 19034

Drug: Sulfacet (sodium sulfacetamide) Clear Lotion, 10%

Formulation:

Ingredient	mg/g
Sulfacetamide sodium, USP	
Edetic acid	
Hydroxyethyl cellulose, NF	
Lauric myristic 2:1 diethanolamide	
Methylparaben, NF	
Polyethylene glycol 400, NF	
Propylene glycol, USP	
Silicone emulsion	
Sodium chloride, USP	
Sodium bisulfite	
Xanthan gum	
Purified water, USP	

Category: This product is intended for the topical treatment of acne vulgaris. It is to be used 1-3 times daily.

Date of Submission: December 22, 1988. Amendment dated August 8, 1989.

Related Submissions: NDA 5-963, Sodium Sulamyd (sulfacetamide sodium) 10% and 30%. Manufactured by Schering. Also NDA 19-525, FML-Sulfa (sulfacetamide sodium 10% and fluorometholone, 0.1%). Manufactured by Allergan. There are other ophthalmic products (Metimyd, Schering) which contain sulfacetamide sodium in combination with a steroid.

Chemistry Review: In his review dated April 28, 1989, the chemist, Dr. DeCamp, found a number of manufacturing control deficiencies. These deficiencies were informally communicated to the applicant. No additional control submissions have been made to date.

Pharmacology Review: In his review dated February 21, 1989, Mr. Davitt had no objection to approval of the application. He recommended that the Carcinogenesis and Pregnancy subsections of the labeling be revised to conform to sulfonamide class labeling.

Background: Although no NDA has been submitted for it, Dermik already markets a prescription product named Sulfacet-R Acne Lotion. Sulfacet-R contains 10% sodium sulfacetamide and 5% sulfur. Sulfacet-R is indicated for acne vulgaris, acne rosacea and seborrheic dermatitis. The basis for marketing this product without an NDA is not known to us, nor do we know why Dermik has chosen to submit an NDA for Sulfacet plain.

Sodium sulfacetamide is a derivative of sulfanilamide. For the most part, topical sulfonamide therapy is not used because of a high risk of sensitization. However, sodium sulfacetamide has been found to be nonirritating to the eye in concentrations as high as 30%. The drug penetrates rather easily into ocular fluids and tissues. Other sulfonamides which have been used successfully for topical indications include siver sulfadiazine and mafenide acetate (Sulfamylon).

It is expected that topical drugs with an antibacterial effect (such as sodium sulfacetamide) would be useful against inflammatory lesions (papules and pustules). The usefulness of these products against other acne lesions (comedones, cysts) is dependent on their ability to penetrate the skin to the base of the lesion.

Clinical Studies

A. Controlled Clinical Studies (Pivotal Studies)

Investigators: Leonard Swinyer, M.D.
Salt Lake City, Utah

Joel Jurnovoy, M.D.
Broomall, Pennsylvania

Method: Dr. Swinyer and Dr. Jurnovoy conducted two independent studies using identical clinical protocols. The protocol was as follows:

1. Study design: This was a parallel group comparison of Sulfacet Lotion 10% to its vehicle. Patients were assigned to the treatment groups in a random fashion.

2. Patient selection: Males and females with Grade II or III acne (mild to moderate) with a minimum of 10 and a maximum of 100 inflammatory lesions.

3. Patient exclusions: These included patients who did not meet the selection criteria as well as those treated with systemic or topical antibiotics within four weeks of initiation of the study.

4. Dosage and duration: Application of the test products were made twice daily for 10 weeks.

5. Effectiveness parameters: Evaluations were made at the initial visit and at weeks 2, 4, 7 and 10. Counts were made of open and closed comedones, papules and pustules on the face. An overall evaluation (global assessment) was made by the patients at the final visit based on the following scale:

   0 - Worse
   1 - No change
   2 - Slight improvement
   3 - Moderate improvement
   4 - Excellent improvement

   The patients were also asked to evaluate the degree of improvement at the end of therapy. In addition, evaluation of the individual signs and symptoms erythema, peeling, dryness and oiliness was made on a scale of "none", "mild" and "moderate" before therapy was begun and at the end therapy.

6. Safety evaluation: Adverse reactions were monitored at each patient visit.

Results: It is felt that the most important indicators of effectiveness are lesion counts. We will also present the results of the sign and symptom evaluations, and the patient evaluations of global improvement.

1. Dr. Swinyer

   a. Evaluable patients: A total of 59 patients entered the study, and all were evaluated for safety. Six patients dropped out of the study. One had an adverse reaction, which will be discussed in the safety evaluation below. One had a changed diagnosis (from acne vulgaris to acne rosacea). Four left "voluntarily" although it appears that one of these suffered an adverse reaction prior to resigning the study (see safety evaluation).

      We have examined the demographic data for the active and placebo groups and conclude that they are comparable.

   b. Inflammatory lesions: Since so few papules were evaluated in the study, we have added the papule and pustule counts together.

Inflammatory Lesions - Mean Number and % Change from Baseline

Treatment Group	Baseline	Week 2	Week 4	Week 7	Week 10	Number Patients
Sulfacet	30.9	29.4(5%)	21.3(31%)	18.3(41%)	14.1(54%)	27
Vehicle	31.8	31.4(1%)	29.8(6%)	23.7(25%)	21.4(33%)	26

The differences between active and placebo in terms of % reduction in lesions are statistically significant at week 4 (p=0.003) and week 10 (p=0.001).

c. Comedones: Open and closed comedones are combined in this presentation.

Comedones - Mean Number and % Change from Baseline

Treatment Group	Baseline	Week 2	Week 4	Week 7	Week 10	Number Patients
Sulfacet	76.0	82.4(108%)	62.8(17%)	47.6(37%)	38.4(49%)	27
Vehicle	70.2	74.0(2%)	67.6(4%)	49.6(29%)	44.8(36%)	26

None of the differences presented here are statistically significant.

d. Global assessment:

Status of Disease at Week 10 Compared to Baseline

Number of Patients and % of Total

Treatment Group	0	1	2	3	4	Patients
Sulfacet	0	0	5(18%)	13(48%)	9(33%)	27
Vehicle	1(4%)	2(8%)	4(15%)	12(4%)	7(27%)	26

There is no significant difference between the groups.

e. Signs and symptoms.

Sign or Symptom		Sulfacet		Vehicle	
		Initial	Final	Initial	Final
Erythema,	none	11	0	6	0
	mild	13	26	15	26
	moderate	3	1	4	0
Peeling,	none	16	7	15	4
	mild	10	19	7	22
	moderate	1	1	3	0
Dryness,	none	4	4	2	3
	mild	16	18	19	21
	moderate	7	5	4	2

Sign or Symptom	Sulfacet		Vehicle	
	Initial	Final	Initial	Final
Oiliness, none	5	11	5	10
mild	18	15	18	14
moderate	4	1	2	2

One vehicle patient was not present for the initial evaluation. The data presented here do not display a significant difference between the active and placebo drug groups.

f. Safety evaluation: One patient on placebo who swam daily in chlorinated water "appeared" to be developing cystic acne and very dry skin. One patient on active dropped himself from the study, reporting by phone that his face had "really broken out", but he refused to return for a subsequent exam. A second patient on active developed an irritant eczema on the face. The irritation cleared when medication was stopped.

g. Effectiveness evaluation: This study demonstrates that Sulfacet is superior to its placebo in mild to moderate acne. Although the active product was superior in the most important parameter for drugs of this type (inflammatory lesion counts), none of the other parameters tested demonstrated a difference between active and placebo.

2. Dr. Jurnovoy

a. Evaluable patients: A total of 54 patients entered the study, and all were evaluated for safety. Two patients in the vehicle group were not evaluated for efficacy because of noncompliance with the treatment schedule.

We have examined the demographic data for the active and placebo groups and conclude that they are comparable.

b. Inflammatory lesions:

Inflammatory Lesions - Mean Number and % Change from Baseline

Treatment Group	Baseline	Week 2	Week 4	Week 7	Week 10	Number Patients
Sulfacet	16.7	11.6(31%)	9.6(43%)	7.2(57%)	7.7(54%)	27
Vehicle	17.6	17.0(3%)	15.9(12%)	12.9(27%)	11.1(37%)	25

The differences between active and placebo in terms of % reduction in lesions are statistically significant at all treatment weeks. However, it can the seen that the gap between the active and placebo groups narrows. At week 10, the p value is 0.01 for difference in % reduction of lesions. In terms of actual reduction (number of lesions rather than % reduction) the difference is on the borderline of significance at week 10 (p = 0.05).

c. Comedones:

Comedones - Mean Number and % Change from Baseline

Treatment Group	Baseline	Week 2	Week 4	Week 7	Week 10	Number Patients
Sulfacet	16.3	14.2(13%)	13.1(20%)	11.9(27%)	9.9(39%)	27
Vehicle	18.0	17.5(3%)	17.5(3%)	16.2(10%)	14.4(20%)	25

None of the differences presented here are statistically significant.

d. Global assessment:

Status of Disease at Week 10 Compared to Baseline

Number of Patients and % of Total

Treatment Group	0	1	2	3	4	Patients
Sulfacet	0	2(7%)	6(22%)	17(63%)	2(7%)	27
Vehicle	0	8(32%)	15(60%)	2(8%)	0	25

The difference between the groups is statistically significant at a level of p = 0.0001.

e. Signs and symptoms:

Sign or Symptom		Sulfacet		Vehicle	
		Initial	Final	Initial	Final
Erythema,	none	16	23	18	22
	mild	11	4	7	3
	moderate	0	0	0	0
Peeling,	none	27	25	27	25
	mild	0	0	0	0
	moderate	0	0	0	0

Sign or Symptom		Sulfacet		Vehicle	
		Initial	Final	Initial	Final
Oiliness,	none	16	7	16	7
	mild	11	16	8	15
	moderate	0	4	1	3

Dryness was not rated by this investigator. The other parameters do not display a significant difference between the active and placebo groups.

f. Safety evaluation: There were no adverse reactions reported during the study.

g. Effectiveness evaluation: This is a study in which marginal effectiveness of the active product vs. the placebo is shown at the end of the study. While statistical significance is present in the global evaluations, we do not place as much reliance on evaluations done by the patients themselves as on evaluations done by the clinical investigator.

A. Special Studies (Studies to determine irritation, sensitization, photo-irritation and photo-sensitization potential of the drug).

Investigator: All four studies were performed by:
Kays Kaidbey, M.D.
Philadelphia, PA 19104

1. Contact - sensitization (Maximization assay)

Method: Twenty-six healthy adults were studied. This test consists of 3 phases: pre-testing, induction and challenge. In the pre-testing phase, approximately 0.1ml of the test drug is applied to the upper outer arm and occluded. The patch is left in place for 48 hours. It is then removed and examined for signs of irritation. In this case, none was seen, except in one patient as described below.

In the induction phase, 0.1ml of 1.5% aqueous sodium lauryl sulfate solution is applied to the test site and occluded for 24 hours. The patch is then removed and 0.1ml of the test drug is applied to the same site and occluded again, this time for 48 hours. The patch is then removed and examined for irritant reactions. In this case, all subjects displayed a moderate irritant reaction. The test drug was then reapplied to the same test site and occluded for 48 more hours. A total of 5 induction exposures were given.

In the challenge phase, the subject is rested for 10 days and then challenged with a single application of the test drug to a new test site on the opposite arm. The site is occluded for 48 hours and then graded for sensitizaton.

Results: None of the test subjects displayed sensitization reactions. However, one subject was dropped from the pre-testing phase because of a reaction. The sponsor was asked for details of this reaction. The patient was a healthy 28-year old female who had no previous history of allergies. She developed erythema and some induration after the first 48-hour "pre-test" phase.

It seems obvious that this is a primary allergic reaction (possibly better classified as irritant reaction, since the patient was not challenged). Thus, the true results of the study are that 1/26(4%) of the subjects suffered an irritant reaction to the drug prior to the induction phase.

2. 21- day irritation/sensitization assy

Method: Twenty-eight healthy adults were studied. This test consists of 2 phases: induction and challenge. In the induction phase, 0.1ml of the test material is applied to a test site on the arm and occluded for 24 hours. At the end of each 24-hour test period, the test site is graded for irritant reactions, the test drug is reapplied, and the process is repeated for a period of 3 weeks. The irritancy is graded on a scale of 0 = none to 4 = intense.

In the challenge phase, the patient is rested for a week and the test drug applied to a new test site on the opposite arm. The sites are occluded for 48 hours and examined for contact sensitivity. This process is repeated one more time.

Result: Ths irritancy scores were added for each patient and the mean calculated. The mean was 4.9, which is a relatively low score over the 3-week course of the study. No contact sensitivity was demonstrated.

3. Phototoxicity bioassay

Method: Ten healthy adults were studied. The lower midback served as the testing site. 50ul of the test drug is put on the test sites (one active, one control) and allowed to rest for 10 minutes. The sites are then occluded for 6 hours. One dressing is then removed and the site exposed to UVA and visible light. Reactions are graded immediately and at 24 and 48 hours.

Results: No phototoxicity reactions were observed.

4. Photocontact allergenicity

Method: Twenty-seven healthy adults were studied. The lower back served as the test site. 10ul of the test drug is put on the test site and occluded for 24 hours. The sites are then exposed to three minimal erythema doses from a standard light source. The sites are then left open for 24 hours and the procedure repeated. This sequence is done twice weekly for 3 weeks. 10-14 days later, the subjects were challenged at a new test site.

Results: No photocontact allergenicity reactions were noted.

Labeling: We have the following comments concerning the draft package insert:

Summary and Evaluation: Two clinical studies in support of effectiveness were performed, which used BID applications for ten weeks. The studies were parallel double-blind group comparisons of Sulfacet Clear Lotion and its vehicle. The effectiveness parameters tested were inflammatory lesions, comedones, signs and symptoms and patient global assessment.

In both studies, the active product was statistically significantly superior to the placebo in terms of % reduction in inflammatory lesions at the end of therapy. The statistical review by Dr. Taneja of our Biometrics group is in agreement that statistical significance has been achieved in inflammatory lesion reduction. This is the most relevant parameter for acne drugs of this type. However, other parameters did not show a difference between treatment groups except for patient global assessment in one study.

We have historically required that the global evaluation be done by the physician, rather than the patient, in acne studies. This requirement is even more critical in view of the marginal effectiveness of the drug. We therefore cannot recommend approval of this application at this time. Two additional clinical studies which include physician global evaluations are necessary.

The drug appeared to be as safe in clinical studies and irritation and sensitization testing as are other prescription acne products.

Recommendation: This application should not be approved.

David C. Bostwick
Chemist

C. C. Evans M.D.

C. Carnot Evans, M.D.
Group Leader/DERM

cc: Orig NDA
HFD-340
HFD-520
HFD-520/JMDavitt
HFD-520/WHDeCamp
HFD-520/MO/CSO/DCBostwick:elp/08/16/89
5059m

nb 9/89

Pharm/Tox

Review and Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products (HFD-540)

NDA 19-931 (BZ &AZ) (Amendment to a pending application)

Submission Date: March 4 & July 1, 1994

Drug Name: Sulfacet Clear Lotion (sodium sulfacetamide 10%)

Category: A sulfonamide drug (antibacterial)

Indication: Acne vulgaris

Sponsor: Dermik Laboratories, Inc., P.O.Box 1200, Collegeville, PA

Number of Vols.: One

Date CDER Received: 7/11/94

Date Assigned: 8/31/94

Date Review Started: 9/20/94

Date 1st Draft Completed: 10/3/94

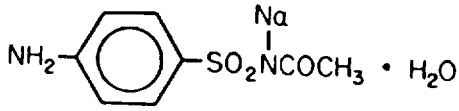
Date Review Accepted by Supervisor: 10/20/94

Related submissions: IND

Review Objectives: To review a rabbit ocular irritation study and an <u>in vitro</u> skin permeation study.

Chemical Name: Acetamide, N-[(4-aminophenyl) sulfonyl], mono-sodium salt, monohydrate

Chemical structure:



<u>Preclinical Study</u>

1. Primary Eye Irritation Study in Rabbits (Project #92-7721A)

Lab Performing Study:

Material Tested: Sulfacet Clear

Species: NZ White rabbit

Procedure: Prior to initiation of the study, the eyes were examined

with fluorescein dye.

A 0.1 ml portion of the test article was instilled into the conjunctival sac of one eye of the test animals, and the other eye remained as an untreated control. The eyes of the animals were not washed after the drug instillation.

The treated eyes were examined at 1, 24, 48 and 72 hours, and at 4 and 7 days following instillation of the test article. The eyes were also examined with fluorescein dye. The ocular lesions were scored according to Modified Draize Technique.

Results: The average ocular irritation scores were:

1 Hour	24 Hours	48 Hours	72 Hours	4 Day	7 Day
1.67	0.00	0.00	0.00	0.00	0.00

The scores indicated that the drug was not an ocular irritant (FHSA). Cornea and iris were not affected. Fluorescein dye tests were negative.

2. "In Vitro Permeation of Sulfacetamide From a Clear Lotion Vehicle"

Lab Performing Study:

Material Tested: Sulfacet Clear Lotion, (control #LMM1-51)

Methods: Frozen human cadaver skin samples obtained from 5 donors and dermatomed to a thickness of approximately 0.25 mm, were thawed, and placed on the Franz cell with the dermis layer facing the buffer in the dermal chamber. The integrity of the skin sections was assured by examining its permeability to tritiated

water.

The test solution (5 l/cm^2 = 525 g of sulfacetamide) was applied to epidermal side of each skin section. At 2, 4, 9, 12, 24, 32 and 48 hours the receptor solution was replaced with fresh buffer. At the end of the experiment the skin samples were washed, and dermis and epidermis layers were separated. All samples collected were analyzed for the drug.

Results:

The attached tables 1 and 2 show the penetration profile of sulfacetamide into the receptor solution and into various skin components. Peak flux was reported to occur within the first two hours after topical application.

Nearly 2 g of the drug penetrated through the stratum corneum into the dermis and the receptor solution, while 97% of the applied dose remained on the surface. There was very high degree of variability in the absorption profile among the different donor's skin samples. The investigators have suggested a possible follicular pathway for the percutaneous absorption of sulfacetamide.

Evaluation:

The initial NDA submission for this product was in December 22, 1988 to HFD-520. The application was found to be non-approvable "because the clinical efficacy studies did not include an acceptable physician global evaluation".

Also, Dr. Lumpkin, the Director of HFD-520 in 1990, found the pharmacology review of Mr. Davitt inadequate at that time. Later,

at the suggestion of Dr. Lumpkin, Dr. Osterberg reexamined the pharmacology/toxicology data, and recommended that the sponsor should perform an eye irritation study in rabbit, and examine the percutaneous absorption of the drug in an in vitro system.

In the present submission, both these completed studies have been submitted.

The results of the eye irritation study showed that the drug product was not an irritant in this test.

The other recommended study to investigate percutaneous absorption from the clinical formulation showed a great variability in the results. The maximum absorption, however, was less than 4% of the applied dose.

The labeling should include the results of these completed studies.

Recommendation:

The application is approvable with labeling change.

Syed N. Alam, Ph.D.

Pharmacologist

cc:

HFD-340

HFD-502/

HFD-540/

HFD-540/Pharm/Alam

10/22/94

HFD-540/MO/Toombs

HFD-520/Micro/Sheldon

HFD-540/Chem/Mokhtari-Rejali

HFD-540/CSO/Turtil

HFD-540/f/t init by SAlam 10/20/94

HFD-540/DD/Concurrence/Wilkin

10/27/94

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-931 (Original Submission, dated 12/30/88)

DATE RECEIVED: 12/23/88

DATE ASSIGNED: 2/21/89 (Archival Copy; triplicate not submitted)

DATE REVIEW COMPLETED: 2/21/89

APPLICANT: Dermik Laboratories, Inc.
Fort Washington, PA

DRUG: Sulfacet[R] Clear Lotion

CATEGORY: Antimicrobial sulfonamide (topical)

RELATED SUBMISSIONS: IND and NDA

COMPOSITION:

Sulfacet® Clear (sodium sulfacetamide) Lotion

Component/Combined Totals	Mg/g
✓Edetic Acid	
✓Hydroxyethyl Cellulose, NF	
✓Lauric Myristic 2:1 Diethanolamide	
✓Methylparaben, NF	
✓Polyethylene Glycol 400, NF	
✓Propylene Glycol, USP	
✓Purified Water, USP	
✓Sodium Chloride, USP	
✓Sulfacetamide Sodium, USP	
✓Xanthan Gum	

COMMENTS AND RECOMMENDATIONS:

1.) This is a [redacted]% sodium sulfacetamide preparation for topical use in the treatment of acne vulgaris.

2.) No preclinical animal studies are reported in this application. Safety evaluation must be based on the results of clinical studies.

3.) The "Carcinogenesis..." and "Pregnancy" sections of the labeling should be revised to conform to sulfonamide class labeling.

John M. Davitt

cc: Orig. NDA 19-931
HFD-340
HFD-502/JWeissinger
HFD-520
HFD-520/Pharm/Davitt
HFD-520/MO/Powell
HFD-520/CSO/Bostwick
HFD-520/Chem/DeCamp
HFD-520/Davitt/kjs/3/3/89
R/d init.by:JMDavitt
1217p

Bio

Action Package

==========

NDA: 19-931 **SUBMISSION DATE:** May 13, 1994

Sodium sulfacetamide, 10% lotion **(Sulfacet[R] Clear Lotion)**

Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

REVIEWER: Funmilayo Ajayi, Ph.D.

TYPE OF SUBMISSION: Original NDA for OTC use **CODE:** 3, S

==========

SYNOPSIS: The purpose of this submission is for a waiver of *in-vivo* bioavailability studies. The application, NDA 19-931, is for a 10% sodium sulfacetamide lotion intended for the treatment of acne vulgaris. It was found to be non-approvable in October of 1985. The sponsor has been in constant correspondence with the Agency and is currently seeking a waiver of the need to demonstrate *in-vivo* bioavailability for this compound. In view of this, the report of an *in-vitro* percutaneous penetration study using human cadaver skin was submitted. The method employed utilized the Franz Diffusion cells with phosphate-buffer saline (pH 7.4) as the receptor fluid and human skin dermatomed to about 0.25 mm thickness as the membrane. The peak flux, 0.73 $\pm$ 0.23 ug/hr/cm^2, occurred within the first 2 hours following application of the lotion. The total penetration of sodium sulfacetamide across the stratum corneum into the dermis and receptor fluid over a period of 48 hours from an applied dose of 525 ug was found to be 1.97 $\pm$ 0.45 ug. Thus, it can be assumed that approximately 1.52 mg will penetrate the skin following application of 4 g of 10% lotion. This translates to about 0.31 ug/ml in a 70 kg person with 70 ml blood / kg. It was also observed that an average of approximately 97 $\pm$ 5% of the applied amount remained on the skin 48 hours after application. Thus, the penetration of sulfacetamide from this formulation through the cadaver skin is very low.

RECOMMENDATION: The submitted report of the *in-vitro* percutaneous penetration study is acceptable to the Division of Biopharmaceutics. However, the comments to the Firm and the labeling comments (page 4) must be adequately addressed.

TABLE OF CONTENTS

ORGANIZATION OF REVIEW: Following the background is a description of the drug formulation, the general comments, and the comments to the Firm.

BACKGROUND: Sodium sulfacetamide is a sulfonamide that possess antibacterial effect against a wide range of gram negative and gram positive organisms. The mechanism of the antibacterial action has been suggested to be due to the competitive antagonist effect of sodium sulfacetamide on para-amino-benzoic-acid (PABA) which is an essential component for bacterial growth. Sodium sulfacetamide has been used as a topical agent in the therapy of ophthalmic infections, acne, and seborrheic dermatitis. It is available as 10% solution, lotion and cream; as well as in 30% solution. The current NDA is for a 10% lotion for the treatment of acne vulgaris. This formulation has not been marketed in the USA or any other country. However, other topical formulations have been marketed for more than 40 years worldwide mainly for ophthalmic use.

DRUG FORMULATION:

Sulfacet® Clear (sodium sulfacetamide) Lotion

Component/Combined Totals	Mg/g	Kg per 200 kg*	%W/V
Edetic Acid			
Hydroxyethyl Cellulose, NF			
Lauric Myristic 2:1 Diethanolamide			
Methylparaben, NF			
Polyethylene Glycol 400, NF			
Propylene Glycol, USP			
Purified Water, USP			
Sodium Chloride, USP			
Sodium Metabisulfite, NF (Sodium Bisulfite)			
Sulfacetamide Sodium, USP			
Xanthan Gum			

* Typical batch size

The average density of Sulfacet Clear Lotion is 1.07.

SUMMARY OF STUDY:

An *in-vitro* percutaneous penetration study using human cadaver skin from 5 donors was performed using Franz Diffusion cells with phosphate-buffer saline (pH 7.4) as the receptor fluid. The human skin were dermatomed to about 0.25 mm thickness and served as the membrane. The peak flux, 0.73 $\pm$ 0.23 ug/hr/cm^2, occurred within the first 2 hours following application of the lotion. The total penetration of sodium sulfacetamide across the stratum corneum into the dermis and receptor fluid over a period of 48 hours from an applied dose of 525 ug was found to be 1.97 $\pm$ 0.45 ug. Thus, it can be assumed that approximately 1.52 mg will penetrate the skin following application of 4 g of 10% lotion. This translates to about 0.31 ug/ml in a 70 kg person with 70 ml blood / kg. It was also observed that an average of approximately 97 $\pm$ 5% of the applied amount remained on the skin 48 hours after application. Although the report indicated low penetration of sulfacetamide from this formulation through the cadaver skin, the extent of exposure to this sulfonamide following prolonged multiple application is unknown.

GENERAL COMMENTS (NEED NOT BE SENT TO THE FIRM)

(i) Blood levels following oral administration of conventional doses has been reported to be about 60 ug/ml of free sulfacetamide (*The Pharmacological Basis of Therapeutics, 3rd Edition,* by Goodman and Gilman). However, blood levels are higher in subjects with renal impairment because the kidneys is the primary route of elimination of this compound. Approximately 70% of a given dose is eliminated in urine within 24 hours and 80 to 90% in 48 hours. The high solubility of sulfacetamide in urine (up to 2%) accounts for the low incidence of crystalluria and other untoward effects on the urinary tract. The clinical use of sulfacetamide was primarily for urinary tract infections - 1 g orally 3 times daily. Sodium sulfacetamide is currently used in the treatment of acne, urinary tract infections, and as ophthalmics.

(ii) From the in-vitro study, it was estimated that a blood concentration of approximately 0.31 ug/ml, ~ 20 times less than that following oral administration of conventional doses, will be achieved following topical aplication of a single dose. However, percutaneous absorption is likely to be higher through the viable skin, bearing in mind the blood supply to the skin and other factors such as disease state.

(iii) The dosing recommendation states that a thin film of the lotion be applied 1 to 3 times a day. With a reported half-life of 7 to 8 hours, accumulation of sulfacetamide following multiple topical application should be negligible.

(iv) However, since the duration of use is unlimited and the bioavailability following prolonged topical application of this sulfonamide is unknown, it is recommended that the sponsor, as part of a Phase IV clinical study, determine the blood and urine concentrations of sulfacetamide and its main metabolite during multiple dosing for a period of about 28 days.

(v) There is a need to develop an in-vitro method for assuring comparable batch-to-batch

release of sulfacetamide from the lotion preparation. As a result, the sponsor would be required to make a commitment towards achieving this goal.

LABELING COMMENTS: The clinical pharmacology section should read thus:

COMMENTS TO FIRM:

(i) Because the extent of exposure to this sulfonamide following prolonged multiple application is unknown, it is recommended that the blood and urine concentrations of sulfacetamide and its main metabolite be determined from random samples obtained during multiple dosing for a period of 28 days. This study could be a part of a Phase IV clinical study. The Division of Biopharmaceutics will be happy to review the protocol of such study.

Noted. 6/13/94 9/J

(ii) It is important to develop an in-vitro method and technique for monitoring the rate of release of sodium sulfacetamide from the 10% lotion formulation. This would serve as batch-to-batch quality control. For more information, please refer to the last paragraph of the publication in Pharmaceutical Research (1987), vol.4, No.3, pg. 265.

CMC issue

(iii) The sponsor is required to make a commitment (a) to provide a report of the study described in Item (i) and, (b) to develop an in-vitro method discussed in Item (ii) above and submit a report of the data so generated.

Ajayi 10/3/94

Funmilayo O. Ajayi, PhD
Pharmacokinetics Evaluation Branch II

FT initialled by Frank Pelsor, PharmD.....F. Pelsor.....

cc: NDA 19-931, HFD-540 (Clinical Division), HFD-426 (Fleischer), HFD-427 (M. Chen, Pelsor, Ajayi), Chron, Drug, Reviewer, FOI (HFD-19).

Appendix I
(study summary)

IN VITRO PERMEATION OF SULFACETAMIDE FROM A CLEAR LOTION VEHICLE

Thomas J. Franz and Paul A. Lehman

Department of Dermatology
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Sponsor: Dermik Laboratories, Inc.
Collegeville, PA

OBJECTIVE: To measure the penetration and permeation of sulfacetamide *in vitro* through human skin from a single formulation.

MATERIALS AND METHODS

Formulations: The 10% (w/w) sodium sulfacetamide formulation used in this study was prepared by the sponsor and labeled as "Sulfacet Clear Lotion", control no. LMM1-51

Skin Preparation:

Human trunk skin, from five donors, without obvious signs of skin disease, was used in this study. It was obtained within 24 hours of death, dermatomed to a thickness of approximately 0.25 mm, sealed in a water-impermeable plastic bag, and stored at -70° C until the day of the study. Prior to use it was thawed by placing the bag in 37° C water, then rinsed in tap water to remove any adherent blood or other material from the surface. Skin from each donor was cut into multiple smaller sections big enough to fit on 0.8 cm^2 Franz cells. The dermal chamber was filled with phosphate-buffered saline (PBS), pH 7.4, and the epidermal chamber was left open to the ambient laboratory environment. The chambers were then placed in a diffusion apparatus in which the dermal receptor solution was stirred magnetically at 600 rpm and its temperature maintained at 37° C.

To assure the integrity of each skin section, its permeability to tritiated water was determined before application of the test formulation. Following a brief (0.5-1 hour) equilibration period, 0.15 ml ^3H_2O (specific activity = 0.3 μCi/ml) was layered across the top of the skin section so that the entire exposed surface was covered. After 5 minutes the aqueous layer was removed and the surface of the skin carefully blotted dry. At t=0.5 hour the saline receptor solution was removed and an aliquot assayed for tritium content. Skin specimens in which the 0.5 hour absorption of ^3H_2O was less than 1.25 μl were considered acceptable.

Percutaneous Absorption: Following the measurement of ^3H_2O absorption the test formulation was applied to multiple (4-7) sections from each donor at a dose of 5 µl/cm^2 using a positive displacement pipetter. At 2, 4, 9, 12, 24, 32 and 48 hours the receptor solution was removed in its entirety, replaced with fresh saline, and an aliquot analyzed for drug content by HPLC. Samples not analyzed immediately were stored at -20°C for no more than 72 hours. At 48 hours after drug application the surface of each skin section was washed twice with 0.5 ml aliquots of water and the aliquots combined. The surface wash was diluted 1:100 in water and then assayed for drug content. Following the surface wash, the skin specimen was removed from the chamber and separated into epidermis and dermis by gently teasing with forceps. Each was extracted in one ml water over 24 hours with gentle mixing at room temperature, then centrifuged at 10,000 rpm for 5 minutes to remove tissue debris, and analyzed for drug content by HPLC.

High pressure liquid chromatography: The samples were analyzed on a Hewlett-Packard 1090 series II HPLC with a diode-array detector. The solvent system was 95/5 (v/v) water containing 2% acetic acid / methanol. The solvent was pumped at 0.5 ml/min through an ODS Hypersil (5µm, 100 x 2.1 mm) reverse phase column maintained at 40°C. Eluting peaks were monitored at 270 nm (4 nm bandwidth) referenced to 500 nm (50 nm bandwidth). Sample injection volume was 10 µl. Standard curves were prepared by aliquot dilutions of sodium sulfacetamide (USP RN 78485) in distilled-deionized water. Appendix A includes example standard curves and chromatographs obtained during this study.

Calculations: Raw data calculations were performed using Excel spreadsheets (Appendix C). Data from sections within a given donor were averaged and the mean across donors determined. The applied dose was calculated by converting the concentration in the Sulfacet lotion (10% w/w) to the amount of sulfacetamide applied to the skin by volume. Six replicate weights of 25 µl volumes of Sulfacet lotion determined its density at 0.00105 ± 0.00008 g/µl. This showed that 525 micrograms of sulfacetamide was applied in the 5 µl volume dose to each skin section.

RESULTS

Table 1 and 2 lists the overall summary of results obtained from the 5 donors evaluated (Appendix B includes the water integrity test data; Appendix C includes the individual chamber data, calculations and donor summary tables). Figure 1 shows the penetration profile of sulfacetamide into the receptor solution. Peak flux was observed to occur within the first two hours after topical application. Five hours after application the rate of penetration becomes very low and demonstrates an apparent steady-state like flux for the remainder of the study period (48 hours). From the 5 µl dose, nearly 2 µg sulfacetamide penetrated through the stratum corneum barrier into the dermis and receptor solution. The vast majority (97%) remained on the surface of the skin and was recoverable in the surface wash after 48 hours of topical exposure.

A high degree of variability was noted in the rate of absorption profiles from all donors, particularly in the height of the initial peak. This is shown in Figure 2. Some sections of a given donor's skin showed a large initial peak and others failed to show a distinct peak. Although the exact explanation for the high degree of variability is not known, based on the prior experience of this laboratory with other topical drugs this is an unusual observation.

The data suggest that sodium sulfacetamide permeation may largely be controlled by the length of time the vehicle remains intact on the surface of the skin, and the initial peak seen during the first few hours could represent that fraction of the applied dose that has partitioned into the skin from the liquid vehicle. Following loss of solvent from the formulation, through volatilization or movement into the skin, sodium sulfacetamide is no longer present in soluble form and now can move into the skin only after it has been solubilized by the sebum layer on the surface of the skin. The very low rate of absorption seen after 10 hours (0.015-0.019 $\mu g/cm^2/hr$) may, in fact, reflect the slow rate of solubilization of microcrystalline drug.

Another explanation for the kinetic profile of sodium sulfacetamide absorption seen in this study is follicular diffusion. It is possible that the early peak represents absorption of drug that has been deposited over follicles and, once that source has been depleted, drug which is deposited over interfollicular areas must either: 1) diffuse laterally to reach follicles, or 2) diffuse through unbroken stratum corneum. In the first case the rate of absorption would decrease after the initial peak because of an effective lengthening of the diffusion pathway. In the second case the rate of absorption would decrease because of a smaller diffusion coefficient, smaller partition coefficient, or both.

That the follicular pathway of absorption may be important for sodium sulfacetamide is suggested by the large section to section variability seen with each of the donor skins. Since one section of skin may have a greater number of follicles than another or, perhaps, some follicles may be more open than others, a large degree of variability would be expected. This effect would be particularly prominent if, in fact, drug was unable to permeate the skin except through the follicular pathway.

CONCLUSIONS

1. Penetration through human skin of sodium sulfacetamide from Sulfacet Clear Lotion was rapid with peak flux (0.73 ± 0.23 $\mu g/hr/cm^2$) occurring within two hours of its application.
2. Total penetration over 48 hours from a 5 µl topical dose was found to be 1.97 ± 0.45 µg.

Table 1: Overall Summary of Sulfacetamide Penetration and Distribution (Flux values are µg/hr/cm^2; Recoveries are µg)

Sample	Skin Donor Identification							
	ET (5)[a]	CM (4)	AW (5)	JM (7)	VR (6)	Average	SE	M-Time[b]
1	0.032	0.429	0.766	1.071	1.357	0.731	0.233	1.0
2	0.040	0.054	0.121	0.116	0.145	0.095	0.020	3.0
3	0.012	0.035	0.039	0.043	0.033	0.032	0.005	6.5
4	0.011	0.019	0.024	0.022	0.017	0.019	0.002	10.5
5	0.011	0.026	0.015	0.022	0.021	0.019	0.003	18.0
6	0.007	0.027	0.014	0.020	0.014	0.016	0.003	28.0
7	0.006	0.027	0.012	0.017	0.012	0.015	0.004	40.0
Recpt Penetration:	0.42	1.73	2.02	2.68	3.01	1.97	0.45	
Dermis:	0.08	0.13	0.05	0.21	0.06	0.10	0.03	
Epidermis:	2.47	3.79	1.44	13.40	1.79	4.58	2.24	
Surface Wash:	506.31	493.62	496.23	493.27	557.15	509.31	12.19	
Total Recovery:	509.28	499.27	499.74	509.56	562.00	515.97	11.72	

a. Number of individual sections from each donor.

b. M-time = mid-time of sample interval (hr).

Table 2: **Overall Summary of Sulfacetamide Penetration and Distribution (Percent Recovery of Applied Dose)**

Sample	Skin Donor Identification						
	ET (5)[a]	CM (4)	AW (5)	JM (7)	VR (6)	Average	SE
Recpt Penetration:	0.08	0.33	0.38	0.51	0.57	0.37	0.08
Dermis:	0.02	0.02	0.01	0.04	0.01	0.02	0.01
Epidermis:	0.47	0.72	0.27	2.55	0.34	0.87	0.42
Surface Wash:	96.44	94.00	94.52	93.96	106.12	97.01	2.32
Total Recovery:	97.01	95.10	95.19	97.06	107.05	98.28	2.23

a. Number of individual sections from each donor.

5

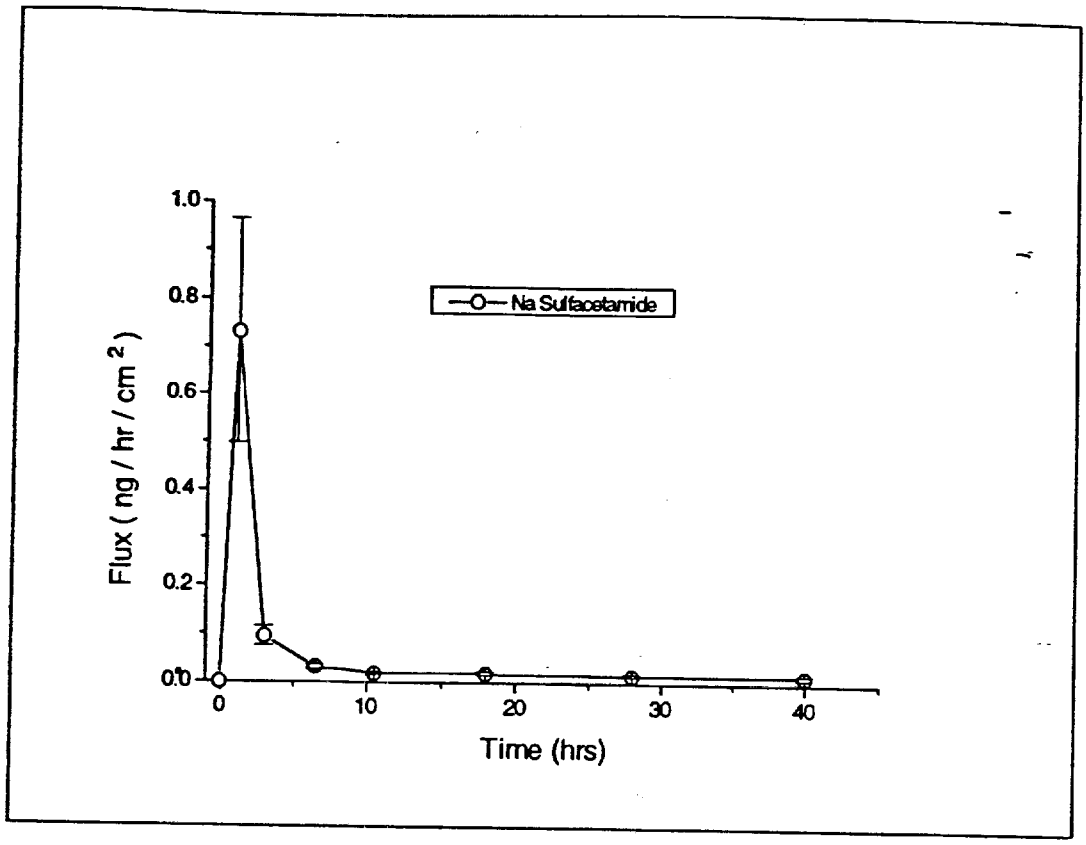


Figure 1: Rate of penetration profile of sodium sulfacetamide into the receptor solution from the topical application of Sulfacet Clear Lotion. Data are mean ± SE from 5 skin donors.

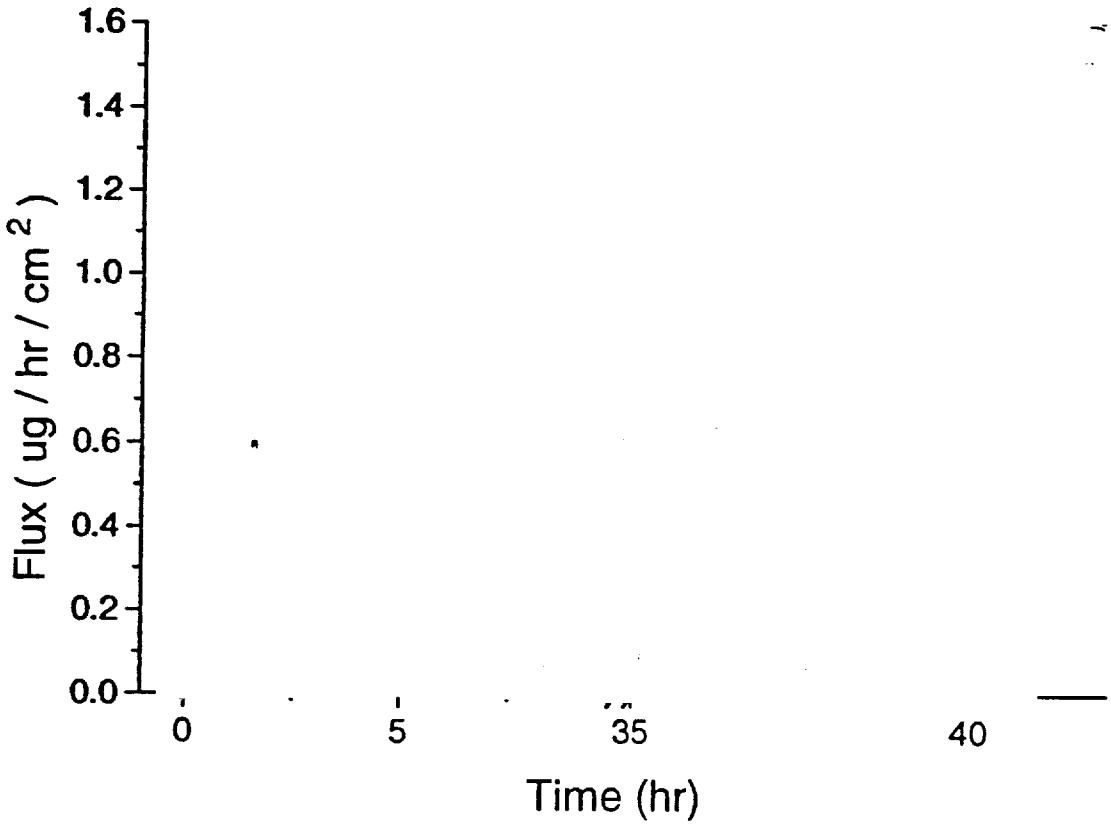


Figure 2: Individual skin penetration averages (dashed lines) and the overall mean flux curve (solid line) for all the skins.

CALCULATIONS TO ESTIMATE PLASMA CONCENTRATIONS OF SODIUM SULFACETAMIDE FOLLOWING TOPICAL ADMINISTRATION

1. The total penetration over 48 hours from a 5 µl (525 µg) topical dose was found to be µg (reference Item 1)

(2 µg / 525 µg) * 100% = 0.38% penetration

2. The recommended dose of a topical lotion is 4 g[1] and 10% of the dose is sodium sulfacetamide.

(4000 mg) * 10% = 400 mg topical dose

3. Assuming 0.38% penetration (1 above), 1.52 mg of a 400 mg dose penetrates.

(400 mg) * 0.38% = 1.52 mg penetrates

4. In a 70 kg patient with 70 ml blood/kg[2], the total blood volume will be 4900 ml.

(70 ml/kg) * 70 kg = 4900 ml

5. If all the dose penetrates simultaneously, the maximum estimated concentration would be 0.31 µg/ml.

(1.52 mg / 4900 ml) * (1000 µg / 1 mg) = 0.31 µg/ml

References:
[1]Arndt, K.A.; Manual of Dermatologic Therapeutics with Essentials of Diagnosis; Little, Brown, and Co., Inc., 1983; page 230 and Table 5.
[2]Diem, K., ed.; Documenta Geigy Scientific Tables, Sixth Edition; Geigy Pharmaceuticals, 1962.

Stat

JUL 29 1994

Statistical Review and Evaluation

NDA#: 19-931

DRUG CLASS: 3-S

Applicant: Dermik Laboratories, Inc.

Name of Drug: Sulfacet Clear Lotion (Sodium Sulfacetamide 10%)

Documents Reviewed: Volumes 2.1 through 2.4 dated April 30, 1994.

Indication: Acne vulgaris

Medical Input: Dr. Ella Toombs, HFD-540

A. INTRODUCTION:

The sponsor first submitted material on this NDA in 1989. Our review of that submission showed sulfacet clear lotion was statistically superior to its vehicle for treatment of inflammatory lesions (papules and pustules) but not comedones. There was neither a patient nor physician assessment of efficacy in the 1989 submission. As a result the medical division requested the sponsor to conduct two additional trials with physician global assessment of efficacy as the primary efficacy variable.

This submission, which has two independent, parallel, double blind trials, is the company's response to that request. In these two trials the sponsor enrolled males and females, ages 13 to 30 years old with grade II or III acne based on the Pillsbury classification plan. Subjects had a minimum of 10 and a maximum

of 60 inflammatory lesions and between 20 and 100 comedones at baseline. The primary efficacy variable was physicians global change from baseline, with measurements being taken at baseline and weeks 2, 4, 6, 8 and 10. Secondary efficacy variables include total inflammatory lesions, comedones and patient's global evaluation.

B. EFFICACY AND SAFETY EVALUATION

STUDY DL 6013-9102

The study conducted under protocol DL-6013-9102 is a single center, double blind, randomized, parallel arm trial comparing sulfacet to its vehicle in the treatment of acne vulgaris. Thirty five subjects were enrolled in each arm.

At baseline there were no significant differences between the treatment arms (sulfacet vs vehicle) relative to age (20 years vs 19 years), gender(15/35 male vs 16/35 female) or race (14/35 vs 16/35; caucasian, 13/35 vs 15/35; black, 8/35 vs 4/35; other). All p values are greater than .15. In addition, there is no statistically significant difference between treatment arms relative to acne duration prior to study entry or skin complexion (fair, medium or dark).

In making my data validity checks, I found that the number of losses, as reported by the sponsor, plus the number of evaluable subjects adds up to more than 35 subjects per arm. Therefore I have constructed my own evaluable and ITT subject data sets.

I used the comedone and inflammable lesion count change from baseline to determine how "losses" would be classified on the physicians global score evaluation. If there was only a baseline reading, I recorded a "NO CHANGE" on the physicians global evaluation score. I used LOCF for secondary variables.

I made no comparisons based on age since all subjects, by design, were less than 30 years old. Nor did I do any subset analyses on any of the secondary efficacy variables.

The overall evaluation of physicians global score shows that sulfacet is statistically superior to its vehicle; the difference in response rates is 1.11 units, $p < .02$. For females the difference in response is .96 units, $p < .04$ and for males the difference in response is 1.26 units, $p < .02$. The difference in response rates for males and females is not statistically significant, $p > .10$.

My ethnicity subset comparisons show there is a .09 difference in response rate between caucasians and blacks, which is not statistically significant. I combined Oriental, American Indian, Hispanic and other because individually their numbers were

insufficient for statistical comparisons. There is no statistically significant differences in the three way comparisons.

My comparison of reduction from baseline in inflammatory lesions show a mean difference in reduction of 39.3 lesions, $p < .05$ in favor of sulfacet.

My comparison of reduction from baseline in comedones show a mean difference in reduction of 37.1 lesions, $p < .03$ in favor of sulfacet.

Longitudinal analyses total inflammable lesions and comedones indicate the sulfacet begins to show statistically significantly better response than vehicle by week 6, $p < .05$. Statistical significance is approached at week 4, $p < .1$. Physicians global evaluation scores were provided only at week 10, so no longitudinal analysis was possible.

STUDY DL 6013-9302

The study conducted under protocol DL-6013-9302 is a multiple center, double blind, randomized, parallel arm trial comparing sulfacet to its vehicle in the treatment of acne vulgaris. One-hundred forty subjects were randomized to treatment; 70 subjects per arm.

At baseline there were no significant differences between the treatment arms (sulfacet vs vehicle) relative to age (19.1 years vs 19.2 years), gender(35/70 male vs 38/70 female) or race (60/70 vs 57/70; caucasian, 3/70 vs 4/70; black, 7/70 vs 9/70; other). All p values are greater than .15. In addition, there is no statistically significant difference between treatment arms relative to acne duration prior to study entry or skin complexion (fair, medium or dark).

In making my data validity checks, I again found that the number of losses, as reported by the sponsor, plus the number of evaluable subjects adds up to more than 70 subjects per arm. Therefore I have constructed my own evaluable and ITT subject data sets.

I used the same method for assigning losses a physicians global score as described in study DL-6013-9102 above. I used LOCF for secondary variables.

I made no comparisons based on age since all subjects, by design, were less than 30 years old. Nor did I do any subset analyses on any of the secondary efficacy variables.

In study DL-6013-9102 above a five point physicians global score was used versus a six point scale in this study. Therefore, the

difference in change in improvement scores differ somewhat.

The overall evaluation of physicians global score shows that sulfacet is statistically superior to its vehicle; the difference in response rates is 0.51 units, $p < .05$. For females the difference in response is .56 units, $p < .05$ and for males the difference in response is 0.48 units, $p < .05$. The difference in response rates for males and females is not statistically significant, $p > .10$.

My ethnicity subset comparisons show there is a .05 difference in response rate between caucasians and blacks, which is not statistically significant. I made no other comparisons due to small sample sizes.

My comparison of reduction from baseline in inflammatory lesions show a mean difference in reduction of 14.4 lesions, $p < .05$ in favor of sulfacet.

My comparison of reduction from baseline in comedones show a mean difference in reduction of -2.3 lesions, $p = .8$. Numerically this is in favor of vehicle, but it is not statistically significant.

Longitudinal analysis of total inflammable lesions indicate the sulfacet begins to show statistically significantly better response than vehicle by week 8, $p < .05$. No Statistical significance is shown for comedones. Longitudinal analysis of the Physicians evaluation scores wasn't done because data was provided only at week 10.

ADVERSE EVENTS

Meta analysis of the adverse event rates in the two studies indicate there is no statistically significant difference in overall adverse event rates (15/105 for sulfacet versus 14/105 for vehicle) nor in the discontinuation rate due to adverse events (1/105 for sulfacet versus 4/105 for vehicle).

D. CONCLUSIONS (Which May be Conveyed to the Sponsor)

On the basis of my evaluation of the physicians global scores (the primary efficacy variable), these studies demonstrate that sulfacet clear lotion (Sodium Sulfacetamide 10%) is statistically superior to its vehicle in the treatment of acne vulgaris. On the basis of the secondary variables, these studies statistically support the claim that sulfacet clear lotion is more effective than its vehicle for treatment of inflammatory lesions. The statistical evidence supporting the efficacy claim of sulfacet clear lotion relative to comedones is supported in one study only. However, this was not a condition for demonstrating efficacy.

Relative to the evaluation of differential effects due to gender or race, sulfacet demonstrates equal statistical effectiveness for these sub groups.

Sulfacet clear lotion demonstrates no statistically significantly greater risk relative to adverse events than vehicle.

Ralph Harkins, Ph.D.

Ralph Harkins, Ph.D.
Biomedical Statistician
Group Leader, Group 7

Concur: Dr. Satya D. Dubey 7-28-94

cc:
Orig. NDA-19-931
HFD-540
HFD-540/Ms R. Cook
HFD-540/Dr. Wilkin
HFD-540/Dr. Toombs
HFD-540/Dr. Rand
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-344/Dr. Lisook
Chron.
This review contains 5 pages.

HFD

520

OCT 4 1989

STATISTICAL REVIEW AND EVALUATION

NDA #: 19-931/Drug Class 3C

APPLICANT: Dermick Laboratories, Inc.

NAME OF DRUG: Sulfacet Clear Lotion (sodium sulfacetamide 10%)

INDICATIONS: Treatment of acne vulgaris

DOCUMENTS REVIEWED: Volumes 1.1, 1.4 and 1.5 dated December 22, 1988.

CLINICAL REVIEWER: Mr. David C. Bostwick (HFD-520). This review has been discussed with Mr. Bostwick who is in agreement with the comments and conclusions stated.

BACKGROUND:

Two vehicle-controlled, double-blind, parallel randomized studies (under protocol number DO-1307) were conducted, one under Leonard Swinyer, M. D. and the other under Joel Jurnuvoy, M. D., with the objective of assessing the efficacy of Sulfacet Clear Lotion (sodium sulfacetamide 10%) with its inactive aqueous vehicle in the treatment of grades II and III (Pillsbury Classification) acne vulgaris.

In order to insure 50 completed patients and to allow for dropouts the protocol called for 56 patients: males or females, 13 to 30 years of age, with grade II or III acne, with a minimum of 10 and a maximum of 50 inflammatory lesions (papules and pustules) to be assigned, in a random order, either the active medication (sodium sulfacetamide 10% solution) or the vehicle for a 10-week period with an initial visit and 4 return visits at weeks 2, 4, 7 and 10. A thin film of active medication or vehicle was applied to the face by the patients two times daily. On all visits, the number of comedones (open and closed), papules and pustules on the face were recorded along with an additional evaluation of overall appearance, acne grade, and condition of the skin including erythema, peeling, dryness and oiliness. At final visit, an overall global patients' evaluation was made using the following 5-point scale: worse, no change, slight improvement, moderate improvement, excellent improvement, and patients' comparison with previous medication was also evaluated using the 5-point scale: worse, no difference, slightly better, much better, not applicable (no medication used previously).

The primary criterion of efficacy was the reduction in total inflammatory lesions (sum of

papules and pustules) over time. Secondary criteria were reduction in total comedones, improvement in facial skin condition (erythema, peeling, dryness and oiliness), changes in acne grade and the global assessments at the final visit. For inflammatory lesions and comedones, the following derived variables were used in the analyses:

reduction from baseline = baseline count - count at visit; and

percent reduction from baseline = (reduction from baseline/baseline count) x 100%.

STUDY #1 (DR. SWINYER):

A total of 59 patients were entered into the study. Six patients were excluded: four voluntarily left, one had an adverse reaction, and one discontinued for other reasons. Out of 4 who voluntarily left, 3 left after the initial visit having total comedones of 5, 14 and 29, and having total inflammatory lesions of 11, 14 and 39 respectively; 1 left after week 7 visit. The person who left after week 7 had 379 total comedones on initial visit, 136 on week 2 visit, 133 on week 4 visit and 82 on week 7 visit; he had 64 total inflammatory lesions on initial visit, 119 on week 2 visit, 173 on week 4 visit and 156 on week 7 visit. The one who had adverse reaction with sulfacetamide left the study after week 2 visit. She had 22 total comedones on initial visit and 29 on week 2 visit; she had 13 total inflammatory lesions on initial visit and 19 on week 2 visit. The one who left for other reasons (not explained by the sponsor) left the study after week 2 visit. He had 13 total comedones on initial visit and 3 on week 2 visit; he had 23 total inflammatory lesions on initial visit and 49 on week 2 visit. Fifty-three patients completed the study and were evaluated for efficacy; 27 patients received sulfacetamide and 26 received vehicle.

The two groups were comparable (see Table 1) at baseline, and no significant differences were observed with respect to sex, race, age, height, weight, complexion, duration of acne, acne-grade and skin-condition (erythema, peeling, dryness, oiliness).

At week 10 (see Table 2), there was a significant (p=.0429)[1] mean reduction in the number of inflammatory lesions in the sulfacetamide group compared with the vehicle group. The mean percent reduction from the baseline in total number of inflammatory lesions was significantly (p=.0011) greater for the sulfacetamide group than the vehicle group.

There were no significant differences (see Table 2) between the sulfacetamide group and vehicle group for other efficacy variables including number of comedones, acne-grade, and skin condition (erythema, peeling, dryness, oiliness), and global patients' evaluation.

[1]Hereafter all the p-values are for two-sided tests.

STUDY #2 (DR. JURNUVOY):

A total of 54 patients were entered into the study: 27 in sulfacetamide group and 27 in vehicle group. Two patients from vehicle group were not analyzed for efficacy because of the non-compliance with the treatment schedule. One missed week 8 visit and the other dropped after week 4 visit. The one who missed week 8 visit had 10 total comedones on initial visit, 11 on week 2 visit, 9 on week 4 visit and 6 on week 10 visit; she had 14 total inflammatory lesions on initial visit, 13 on week 2 visit, 11 on week 4 visit, and 8 on week 10 visit. The one who dropped after week 4 visit had 20 total comedones on initial visit, 15 on week 2 visit and 11 on week 4 visit; he had 16 total inflammatory lesions on initial visit, 12 on week 2 visit and 12 on week 4 visit.

The two groups were comparable at baseline, and no significant differences (see Table 3) were observed with respect to sex, race, complexion, age, height, weight, duration of acne, acne-grade and skin-condition (erythema, peeling, oiliness).

At week 10 (see Table 4), there was a significant (p=.0458) mean reduction from the baseline in the number of inflammatory lesions in the sulfacetamide group compared with the vehicle group. The mean percent reduction from the baseline in number of inflammatory lesions was significantly (p=.0103) greater for the sulfacetamide group than the vehicle group. For the global patients' evaluation, sulfacetamide group reported a significantly (p=.0001) better response than the vehicle group.

There were no significant differences (see Table 4) between the sulfacetamide group and vehicle group for other efficacy variables including reduction from baseline in number of comedones, percentage reduction from baseline in number of comedones, acne-grade and skin-condition (erythema, peeling, oiliness).

REVIEWER'S ANALYSIS

The protocol appears to state that total number of lesions is the primary efficacy variable but the sponsor did not analyze this variable. However, the sponsor has emphasized positive results for total number of inflammatory lesions (which appears to be secondary efficacy variabble in the protocol). This reviewer analyzed the total number of lesions for the two studies and results are as follows.

STUDY #1 (DR. SWINYER):

The results are given in Table 5. The two groups are comparable at baseline with respect to the total number of lesions as no significant (p=.8440) difference is observed.

At week 10, there are no significant differences between the two groups for total number of

lesions (p=.2944) or for reduction from baseline in total number of lesions (p=.2113); however, there is a significant (p=.0101) percent reduction from baseline in total number of lesions in the sulfacetamide group as compared with the vehicle group.

STUDY #2 (DR. JURNUVOY):

The results are given in Table 6. The two groups are comparable at baseline with respect to the total number of lesions as no significant difference (p=.6023) is observed.

At week 10, total number of lesions is significantly (p=.0340) smaller for sulfacetamide group; percent reduction from baseline in total number of lesions is significantly (p=.0340) greater for sulfacetamide group. However, there is no significant (p=.0777) difference between the two groups for reduction in total number of lesions from the baseline.

REVIEWER'S COMMENTS AND CONCLUSIONS(Which May be conveyed to the Sponsor):

1. The primary and secondary efficacy variables were not explicitly defined in the protocol. The protocol appears to state that the primary efficacy variable is the reduction in the total number of lesions from the baseline, and secondary efficacy variables are reduction in total comedones from baseline, reduction in total inflammatory lesions from baseline, global assessment and comparison with a prior therapy at the final visit. The sponsor did not analyze the primary efficacy variable (reduction in the total number of lesions). The sponsor has emphasized one of the secondary efficacy variables (total number of inflammatory lesions) and has presented favorable results.

2. There were no significant differences between sulfacetamide and vehicle groups for the mean reduction in total number of lesions (the primary efficacy variable) in the two studies: Dr. Swinyer's study (p=.2113) and Dr. Jurnuvoy's study (p=.0777). However, other ways of expressing this primary efficacy variable (e.g., percent reduction from baseline) produced more favorable results ($p \leq .034$). In the absence of an a priori declaration of how this variable should be analyzed the results are at best marginally in favor of sulfacetamide.

3. A significant ($p \leq .0458$) mean reduction from the baseline in the number of inflammatory lesions (one of the secondary efficacy variables) was achieved with sulfacetamide compared with vehicle in both studies. This significance is marginal (borderline) as p-values are close to .05.

4. The mean percent reduction from the baseline in the number of inflammatory lesions (one of the secondary efficacy variables) was significantly ($p \leq .0103$) greater with

sulfacetamide than with vehicle in both studies.

5. In Dr. Jurnuvoy's study, global patients' evaluation and comparison with prior therapy (two of the secondary efficacy variables) showed a significant ($p \leq .0001$) preference for sulfacetamide, but in Dr. Swinyer's study, no significant difference between the two groups was found for these variables. Both of these variables were rated by patients and not by physicians. This introduced a lot of variation in data. In the presence of such a large variation, important effects may be wholly or partially obscured or conversely sponsor may be misled into believing in effects that do not exist. Such confusing effects can be greatly reduced if a physician rates all the patients using a reliable and valid instrument. This increases the probability that the sponsor will be led along a true rather than a false path.

6. There were no significant differences between sulfacetamide and vehicle for other efficacy variables including reduction from baseline in number of comedones, percentage reduction from baseline in number of comedones, acne-grade and skin-condition (erythema, peeling, dryness, and oiliness) in both studies.

7. There exists no explanation of why the exclusion criterion was different for the two studies. In Dr. Swinyer's study, patients were excluded if they had more than 50 inflammatory lesions whereas in Dr. Jurnuvoy's study, they were excluded if they had more than 100 inflammatory lesions.

8. There exists no explanation of why the timing of one of the return visits was different for the two studies. In Dr. Swinyer's study, patients visited in week 7 and in Dr. Jurnuvoy's study, they visited in week 8.

9. The clinical reviewer has indicated that the sponsor will be required to conduct additional studies utilizing a physician global evaluation. We would suggest that at least one additional study be requested with a physician's global evaluation in which we require that the sponsor's most impressive result in these studies (a significant ($p \leq .0103$) mean percent reduction from baseline in total inflammatory lesions - a secondary efficacy variable) be replicated along with a significant difference for the physician's global evaluation. The methods of analysis for these variables should be specified clearly and completely in the protocol in advance so as to avoid any concern about post hoc analysis decisions.

Baldeo K. Taneja, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius 9/29/89

Dr. Dubey 10-2-89

cc:
Orig. NDA 19-931
HFD-520
HFD-520/Mr. Bostwick
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Taneja
HFD-344/Dr. Lisook
Chron.
ajd/x0335/SERB/Write Now/NDA 19-931/8-22-89/9-22-89/9-27-89

This review consists of 6 pages plus 6 tables.

TABLE 1: COMPARISON OF TREATMENT GROUPS AT BASE LINE
(DR. SWINYER'S STUDY)

PATIENT CHARACTERISTIC	TREATMENT GROUPS		STATISTICAL TEST	p-VALUE
	SULFACETAMIDE	VEHICLE		
NUMBER OF PATIENTS	27	26	-	-
AGE (IN YEARS)				
MEAN	18.8	19.7	t	0.5707
SD	4.9	5.8		
HEIGHT (IN INCHES)				
MEAN	67.9	68.9	t	0.3919
SD	4	4.2		
WEIGHT (IN LBS)				
MEAN	141.8	146	t	0.6242
SD	28.2	32.4		
DURATION OF ACNE (IN MO)				
MEAN	62.1	78.5	t	0.3242
SD	50.4	68.5		
SEX				
MALES	14	15	CHISQUARE	0.6694
FEMALES	13	11		
RACE				
CAUCASIANS	27	25	CHISQUARE	0.3036
HISPANICS	0	1		
COMPLEXION				
FAIR	14	15	CHISQUARE	0.3649
MEDIUM	11	11		
DARK	2	0		
ACNE-GRADE				
GRADE II	25	22	CHISQUARE	0.3595
GRADE III	2	4		
ERYTHEMA*				
NONE	11	6	CHISQUARE	0.4313
MILD	13	15		
MODERATE	3	4		
PEELING*				
NONE	16	15	CHISQUARE	0.4755
MILD	10	7		
MODERATE	1	3		
DRYNESS*				
NONE	4	2	CHISQUARE	0.4344
MILD	16	19		
MODERATE	7	4		
OILINESS*				
NONE	5	5	CHISQUARE	0.7443
MILD	18	18		
MODERATE	4	2		
TOTAL NUMBER OF COMEDONES*				
MEAN	76	70.2	t	0.7424
SD	71.7	53.8		
TOTAL NUMBER OF INFLAMMATORY LESIONS*				
MEAN	30.9	31.8	t	0.8892
SD	21.2	24.5		

*: DATA WAS NOT RECORDED FOR ONE PATIENT IN VEHICLE GROUP.

TABLE 2: COMPARISON OF TREATMENT GROUPS AT WEEK 10
(DR. SWINYER'S STUDY)

PATIENT CHARACTERISTIC	TREATMENT GROUPS		STATISTICAL TEST	p-VALUE
	SULFACETAMIDE	VEHICLE		
NUMBER OF PATIENTS	27	26	-	-
TOTAL NUMBER OF COMEDONES				
MEAN	38.4	44.8	t	0.5289
SD	42.3	29.9		
TOTAL NUMBER OF INFLAMMATORY LESIONS				
MEAN	14.1	21.4	t	0.0429
SD	10.4	14.7		
PERCENTAGE REDUCTION FROM BASELINE IN TOTAL COMEDONES				
MEAN	50	16.6	t	0.105
SD	29.7	97.4		
PERCENTAGE REDUCTION FROM BASELINE IN TOTAL INFLMMATORY LESIONS				
MEAN	52.6	26.5	t	0.0011
SD	24.8	30.2		
ACNE-GRADE				
GRADE I	0	0	-	-
GRADE II	27	26		
GRADE III	0	0		
ERYTHEMA				
NONE	0	0	CHISQUARE	0.3218
MILD	26	26		
MODERATE	1	0		
PEELING				
NONE	7	4	CHISQUARE	0.3643
MILD	19	22		
MODERATE	1	0		
DRYNESS				
NONE	4	3	CHISQUARE	0.4402
MILD	18	21		
MODERATE	5	2		
OILINESS				
NONE	11	10	CHISQUARE	0.8201
MILD	15	14		
MODERATE	1	2		
GLOBAL PATIENTS' EVALUATION				
WORSE	0	1	CHISQUARE	0.4958
NO CHANGE	0	2		
SLIGHT IMPROVEMENT	5	4		
MODERATE IMPROVEMENT	13	12		
EXCELLENT IMPROVEMENT	9	7		
PATIENTS' COMPARISON WITH PREVIOUS MEDICATION				
WORSE	1	3	CHISQUARE	0.7036
NO DIFFERENCE	2	2		
SLIGHTLY BETTER	3	5		
MUCH BETTER	14	11		
NOT APPLICABLE	7	5		

TABLE 3: COMPARISON OF TREATMENT GROUPS AT BASELINE
(DR. JURNUVOY'S STUDY)

PATIENT CHARACTERISTIC	TREATMENT GROUPS		STATISTICAL TEST	p-VALUE
	SULFACETAMIDE	VEHICLE		
NUMBER OF PATIENTS	27	27	-	-
AGE (IN YEARS)				
MEAN	18.6	18	t	0.6834
SD	5	4.2		
HEIGHT (IN INCHES)				
MEAN	66.9	65.8	t	0.8293
SD	4.1	4.3		
WEIGHT (IN LBS)				
MEAN	141.3	141.2	t	0.504
SD	30.6	36.2		
DURATION OF ACNE (IN YRS)				
MEAN	5.1	4.9	t	0.8737
SD	4.2	3.8		
SEX				
MALES	16	12	CHISQUARE	0.276
FEMALES	11	15		
RACE**				
CAUCASIANS	26	24	CHISQUARE	0.9557
BLACKS	1	1		
COMPLEXION**				
FAIR	4	5	CHISQUARE	0.5542
MEDIUM	21	17		
DARK	2	4		
ACNE-GRADE**				
GRADE II	24	22	CHISQUARE	0.9202
GRADE III	3	3		
ERYTHEMA**				
NONE	16	18	CHISQUARE	0.3346
MILD	11	7		
MODERATE	0	0		
PEELING**				
NONE	27	25	-	-
MILD	0	0		
MODERATE	0	0		
OILINESS**				
NONE	16	16	CHISQUARE	0.4969
MILD	11	8		
MODERATE	0	1		
TOTAL NUMBER OF COMEDONES**				
MEAN	16.3	18	t	0.552
SD	8.2	11.8		
TOTAL NUMBER OF INFLAMMATORY LESIONS**				
MEAN	16.7	17.6	t	0.6573
SD	7.1	6		

**: DATA WAS NOT RECORDED FOR TWO PATIENTS IN VEHICLE GROUP

TABLE 4: COMPARISON OF TREATMENT GROUPS AT WEEK 10
(DR. JURNUVOY'S STUDY)

PATIENT CHARACTERISTIC	TREATMENT GROUPS		STATISTICAL TEST	p-VALUE
	SULFACETAMIDE	VEHICLE		
NUMBER OF PATIENTS	27	25	-	-
REDUCTION FROM BASELINE IN TOTAL NUMBER OF COMEDONES				
MEAN	6.4	3.6	t	0.242
SD	8.3	8.8		
REDUCTION FROM BASELINE IN TOTAL NUMBER OF INFLAMMATORY LESIONS				
MEAN	9	6.4	t	0.0458
SD	4.4	4.6		
PERCENTAGE REDUCTION FROM BASELINE IN TOTAL COMEDONES				
MEAN	25.6	91.6	t	0.6135
SD	15.9	35.4		
PERCENTAGE REDUCTION FROM BASELINE IN TOTAL INFLMMATORY LESIONS				
MEAN	54.7	35.9	t	0.0103
SD	22.1	28.5		
ACNE-GRADE				
GRADE I	3	3	CHISQUARE	0.993
GRADE II	23	21		
GRADE III	1	1		
ERYTHEMA				
NONE	23	22	CHISQUARE	0.7664
MILD	4	3		
MODERATE	0	0		
PEELING				
NONE	27	25	-	-
MILD	0	0		
MODERATE	0	0		
OILINESS				
NONE	7	7	CHISQUARE	0.952
MILD	16	15		
MODERATE	4	3		
GLOBAL PATIENTS' EVALUATION				
WORSE	0	0	CHISQUARE	0.0001
NO CHANGE	2	8		
SLIGHT IMPROVEMENT	6	15		
MODERATE IMPROVEMENT	17	2		
EXCELLENT IMPROVEMENT	2	0		
PATIENTS' COMPARISON WITH PREVIOUS MEDICATION				
WORSE	1	5	CHISQUARE	0.1326
NO DIFFERENCE	6	9		
SLIGHTLY BETTER	8	4		
MUCH BETTER	2	0		
NOT APPLICABLE	10	7		

TABLE 5: COMPARISON OF TREATMENT GROUPS
(DR. SWINYER'S STUDY)

Patient Characteristic	Treatment Groups		Statistical Test	p-Value
	Sulfacetamide	Vehicle		
Total Number of Lesions at Baseline				
mean	104.36	100.4	t	0.844
sd	89.63	73.13		
sample size	28	28		
Total Number of Lesions at Week 10				
mean	52.52	66.23	t	0.2944
sd	51.89	41.54		
sample size	27	26		
Reduction from Baseline in total number of Lesions at Week 10				
mean	54.41	35.81	t	0.2113
sd	54.15	52.77		
sample size	27	26		
Percent reduction from Baseline in total number of Lesions at Week 10				
mean	51.49	25.64	t	0.0102
sd	24.96	43.47		
sample size	27	26		

TABLE 6: COMPARISON OF TREATMENT GROUPS (DR. JURNUVOY'S STUDY)

Patient Characteristic	Treatment Groups		Statistical Test	p-Value
	Sulfacetamide	Vehicle		
Total Number of Lesions at Baseline				
mean	33.04	35.15	t	0.6023
sd	14.31	15.27		
sample size	27	27		
Total Number of Lesions at Week 10				
mean	17.63	25.08	t	0.034
sd	11.59	13.27		
sample size	27	26		
Reduction from Baseline in Total Number of Lesions at Week 10				
mean	15.41	10.04	t	0.0777
sd	11.22	10.46		
sample size	27	26		
Percent Reduction from Baseline in Total Number of Lesions at Week 10				
mean	45.22	27.88	t	0.034
sd	30.37	27.44		
sample size	27	26		


Chem

DEC - 6 1996

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19931 **CHEM.REVIEW #:** 07 **REVIEW DATE:** 06-DEC-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
FAX AMENDMENT	06-DEC-96	---------	06-DEC-96

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

Proprietary:	Klaron® Lotion
proprietary/USAN:	Sodium Sulfacetamide
Code Names/#'s:	SCL-10
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: for the topical control of acne vulgaris

DOSAGE FORM:	Lotion
STRENGTHS:	10%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_XXX_ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
254.24
CAS 6209-17-2
Sulfacetamide Sodium (USAN)
Refer to USAN for more details.

SUPPORTING DOCUMENTS:

Refer to Chemist's review #1,#2, #3, #4, #5 and #6.

REMARKS/COMMENTS:

The applicant has FAXED a mock up copy of the container and carton labels for Klaron which have been edited for consistency with the revised draft package insert submitted on December 5, 1996. As discussed with Dermik via phone today, Dermik agrees to implement these changes to the next printing. The agreement to implement the cited changes on the container/carton in the next printing is acceptable.

Conclusion:

The applicant has responded to all chemistry concerns cited in the deficiency letter dated June 19, 1996. An acceptable EER has been provided by the Office of Compliance on 11/14/96. The responses have been adequate and an approval action is recommended from a chemistry point of view.

Janet G. Higgins 12/6/96
Janet G. Higgins
Reviewing Chemist

cc: Orig. NDA 19-931
HFD-540/Division File
HFD-540/Higgins
HFD-540/MO/Toombs
HFD-540/Pharm/Alam
HFD-540/Micro/Creedon
HFD-540/CSO/White
HFD-540/SUPERVISOR/DeCamp WD 12/6/96
R/D Init by: SUPERVISOR
filename: N19931.R07

12/21/96

NOV 25 1996

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19931 **CHEM.REVIEW #:** 06 **REVIEW DATE:** 14-NOV-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT\AL	03-JUL-96	05-JUL-96	23-JUL-96
AMENDMENT\NC	23-AUG-96	29-JUL-96	12-SEPT-96
AMENDMENT\AC	26-AUG-96	27-AUG-96	12-SEPT-96
CONSULT	16-OCT-96	---------	
AMENDMENT\BL	25-OCT-96	28-OCT-96	06-NOV-96

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

Proprietary:	Klaron® Lotion
proprietary/USAN:	Sodium Sulfacetamide
Code Names/#'s:	SCL-10
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: for the topical control of acne vulgaris

DOSAGE FORM:	Lotion
STRENGTHS:	10%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	XXX Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
254.24
CAS 6209-17-2
Sulfacetamide Sodium (USAN)
Refer to USAN for more details.

SUPPORTING DOCUMENTS:

Refer to Chemist's review #1,#2, #3, #4 and #5.

REMARKS/COMMENTS:

The applicant has responded to the not approvable letter dated June 19, 1996. Their response was a full response and is outlined in the submissions stated above. Along with their response to the deficiency letter, the applicant selected a new trade name (Klaron® Lotion) for this product. A trade name consult was requested from the Labeling and Nomenclature

Committee on 9/10/96. The committee found no reason for this name to be unacceptable on 10/16/96. This reviewer concurs.

As stated in the not approval letter the major chemistry concern was failure to meet GMP standards. The Case Management and Policy Guidance Branch has requested that this reviewer ask for the following information prior to approving this NDA:

1. An updated manufacturing procedure describing the equipment to be used and mixing/holding times.

2. New accelerated-condition stability data from a recently manufactured lot and a commitment to conduct labeled storage condition studies on the first three full-scale commercial production lots.

The above information was provided in July 3, 1996 submission. The applicant has provided an updated master formula, as attachment 2 in the July 3, 1996 submission. The applicant has stated that the formula will remain restricted until the NDA is approved and validation is complete. Bulk holding times will be determined during the validation, and the master formula will then be further revised. The master formula is presently being updated with the product name, Klaron® Lotion.

It should be noted that the updated manufacturing procedure has increased the batch size from 200.0 Kg to 700.0 Kg. The investigator, Denise M. Digiulio, was contacted on 11/4/96 in order to reveal the size of the biobatch utilized in this NDA. She informed me that the size of the biobatch was 200 Kg. Therefore, this increase to 700.0Kg is acceptable as long as the process validation is completed and found to be acceptable by the district.

The applicant noted that no new lots of this product have been recently manufactured, therefore, Dermik does not have any new accelerated stability data. However, Dermik has committed to conduct accelerated-scale commercial production lots.

The October 25, 1996 amendment contains a revised draft package insert. This submission contains a new draft package insert which appropriately lists sodium metabisulfite as an ingredient. The brand name Sulfacet Clear Lotion has also been changed to Klaron Lotion. All these changes are appropriate and found to be acceptable.

Conclusion:

The applicant has responded to all chemistry concerns cited in the deficiency letter dated June 19, 1996. An acceptable EER has been provided by the Office of Compliance on 11/14/96. The responses have been adequate and an approval action is recommended from a chemistry point of view.

Janet G. Higgins 11/15/96
Janet G. Higgins
Reviewing Chemist

cc: Orig. NDA 19-931
HFD-540/Division File
HFD-540/Higgins
HFD-540/MO/Toombs
HFD-540/Pharm/Alam
HFD-540/Micro/Creedon
HFD-540/CSO/White
HFD-540/SUPERVISOR/DeCamp WA 11/19/96
R/D Init by: SUPERVISOR
filename: **N19931.R06**

JW 11/25/96

Consult #672 (HFD-540)

KLARON sodium sulfacetamide lotion 10%

The Committee found no look-alike/sound-alike conflicts nor any misleading and fanciful aspects with the proposed proprietary name.

The LNC has no reason to find the proposed name unacceptable.

D C Boring 10/16/96, Chair
CDER Labeling and Nomenclature Committee

D 1 /

FEB 4

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19931 **CHEM.REVIEW #:** 05 **REVIEW DATE:** 05-SEPT-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
EER	08-AUG-95	08-AUG-95	N/A

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

Proprietary:	Sulfacet Clear Lotion
Nonproprietary/USAN:	Sodium Sulfacetamide
Code Names/#'s:	SCL-10
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: for the topical control of acne vulgaris

DOSAGE FORM:	Lotion
STRENGTHS:	10%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	XXX Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
254.24
CAS 6209-17-2
Sulfacetamide Sodium (USAN)
Refer to USAN for more details.

SUPPORTING DOCUMENTS:

Refer to Chemist's review #1,#2, #3 and #4.

REMARKS/COMMENTS:

Dermik Labs, a wholly-owned subsidiary of Rhone-Poulenc Rorer, is the applicant of the subject NDA.
which was the contract manufacturer and QC support for Dermik Labs acquired Dermik Labs in late 1994. Due to the various business dealing between these three companies, the inspection was delayed. An establishment evaluation request (EER#6765) was filed on August 19, 1994. The Office of Compliance concurred with the District's recommendation to withhold approval for on August 30, 1995.

The Case Management and Policy Guidance Branch justified their decision to recommend withholding approval of this NDA based on the following findings:

1. The NDA does not contain some essential and basic attributes of the manufacturing process, e.g., the specific equipment to be used and the mixing and bulk product holding times.

2. Some of the referenced stability data (labeled storage condition) for four stability lots which are presented in the NDA are not available. Of these four, all assay chromatograms are missing for one lot and the 0, 1, and 3 month timepoint assay chromatograms are missing for the other three. Thus, the accuracy of the reported data and true stability profile of the formulation cannot be verified.

The Case Management and Policy Guidance Branch has requested that this reviewer ask for the following information prior to approving this NDA:

1. An updated manufacturing procedure describing the equipment to be used and mixing/holding times.

2. New accelerated-condition stability data from a recently manufactured lot and a commitment to conduct labeled storage condition studies on the first three full-scale commercial production lots.

It is the recommendation of this reviewer that we honor the request of the Case Management and Policy Guidance Branch and ask for the information stated above.

There were various other observations made by the investigators of the facility during their inspection which was held from May 1, 1995 to June 23, 1995. Deficiencies with respect to deviations from cGMP's at included:

1. Laboratory Operating Procedures allow for use of the "Outlier Test", out of specification and within specification analytical data are averaged to obtain data which is in specification
2. The evaluation and correction of out of specification results were inadequate
3. quality systems failed to provide for the rejection or handling of product not complying with specifications.
4. current analytical methods lack sufficient precision
5. accuracy and/or ruggedness for use as quantitative regulatory procedures was not adequate

6. current manufacturing process validation reports were incomplete
7. incomplete data was provided to support the validation of some finished product and raw material microbiological test methods including distilled water
8. manufacturing records failed to accurately reflect the processing of the drug product
9. the facilities and equipment are not designed to minimize microbial contamination.

It should also be noted that the production process was not sufficiently described in the filing, lack of development data to support the filed rework process, the microbiological test procedure for the finished product was not validated, and review of the raw stability data revealed inaccuracies.

CONCLUSIONS & RECOMMENDATIONS:

The application is NOT APPROVABLE for manufacturing and controls under section 505 of the Act. The facilities have been inspected and the FDA form 483 that was issued. For more details and additional information please refer to the attached documentation.

The following data should be submitted before the approval of this NDA:

1. An updated manufacturing procedure describing the equipment to be used and mixing/holding times.

2. New accelerated-condition stability data from a recently manufactured lot and a commitment to conduct labeled storage condition studies on the first three full-scale commercial production lots.

Janet G. Higgins 9/5/95
Janet G. Higgins
Reviewing Chemist

cc: Orig. NDA 19-931
HFD-540/Division File
HFD-540/Higgins
HFD-540/MO/Toombs
HFD-540/Pharm/Alam
HFD-540/Micro/Creedon
HFD-540/CSO/Turtil
HFD-540/SUPERVISOR/DeCamp WD 1/19/96
R/D Init by: SUPERVISOR
filename: N19931.R05

JGH 2/14/96

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19931 **CHEM.REVIEW #:** 04 **REVIEW DATE:** 07-APR-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
DRAFT LABELING	N/A	N/A	N/A
METHODS VALIDATION/NC	30-JAN-95	31-JAN-95	N/A
AMENDMENT/XR	27-FEB-95	28-FEB-95	N/A
AMENDMENT/BC	10-MAR-95	17-MAR-95	N/A

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

Proprietary:	Sulfacet Clear Lotion
Nonproprietary/USAN:	Sodium Sulfacetamide
Code Names/#'s:	SCL-10
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: for the topical control of acne vulgaris

DOSAGE FORM:	Lotion
STRENGTHS:	10%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	xxx **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
254.24
CAS 6209-17-2
Sulfacetamide Sodium (USAN)
Refer to USAN for more details.

SUPPORTING DOCUMENTS:

Refer to Chemist's review #1,#2 and #3.

REMARKS/COMMENTS:

There exists three unresolved issues in the subject NDA -- satisfactory inspections, acceptable labeling.

An establishment evaluation request was filed by Dr. Rejali on August 19, 1994 and has remained in pending status. I contacted the investigator of the foreign facility, He informed me that a 483 form was issued to the facility and stated that he would fax me a copy of the 483. The inspection seemed to show no problems of great concern and the applicant can probably address the issues which were brought up

with no major delay. Refer to the attached copy of the issued 483. Shirnette Ferguson from the Office of compliance has contacted the Philadelphia district regarding the subject application and an inspection has not been done, but the assignment has been issued to an investigator. Refer to the attached e-mail. On April 6, 1995, Inspector Denise Digiulio called me from the Philadelphia District and informed me that the Rorer facility would be inspected the week of April 17, 1995.

The methods validation package was never sent off to the St. Louis District for validation. However, according to the applicant and Hank Drew, from the St. Louis Laboratories, the validation was completed and found satisfactory. Mr. Drew said that he would have a copy of the validation package sent to me. I received the MV package on 2/21/95.
The following comments were made by the analysis:

The HPLC assay method appears to be suitable for regulatory work. The retention times (Rt) of the peaks obtained by the district were similar to those obtained by the company.

Peaks of Compounds	Rt
sulfanilamide	2.6 min
sulfacetamide	4.9 min
sulfathiazole	9.6 min
p-OH benzoic acid	11.9 min

All requirements for reproducibility, resolution and tailing were met. The analyst also stated and illustrated in the chromatograms which accompanied her comments that the resolution between the peaks also met the requirement.

A review of the draft labeling was conducted on February 16, 1995. The following observations were brought up by this reviewer concerning the draft labeling.

The proposed action on this application is approvable, pending the resolution of the above deficiencies. Also refer to attached telephone memorandum.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable for manufacturing and controls under section 505 of the Act pending satisfactory GMPs and correction of the draft labeling. One of the facilities has been inspected and the FDA form 483 that was issued is attached (attachment I). The other facility is scheduled for inspections the week of April 17, 1995.

Janet G. Higgins 4/7/95
Janet G. Higgins
Reviewing Chemist

cc: Orig. NDA 19-931
HFD-540/Division File
HFD-540/Higgins
HFD-540/MO/Toombs
HFD-540/Pharm/Alam
HFD-540/Micro/Creedon
HFD-540/CSO/Turtil
HFD-540/SUPERVISOR/DeCamp
R/D Init by: SUPERVISOR
filename:N19931.R04

4/7/95

5/2/95

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19931 **CHEM.REVIEW #:** 03 **REVIEW DATE:** 07-DEC-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT/A-1	12-MAY-94	16-MAY-94	28-NOV-94
AMENDMENT/A-2	04-MAR-94	07-MAR-94	28-NOV-94
AMENDMENT/B-2	01-JUL-94	11-JUL-94	28-NOV-94

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

Proprietary:	Sulfacet Clear Lotion
Nonproprietary/USAN:	Sodium Sulfacetamide
Code Names/#'s:	SCL-10
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: for the topical control of acne vulgaris

DOSAGE FORM:	Lotion
STRENGTHS:	10%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	xxx **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: 254.24
CAS 6209-17-2
Sulfacetamide Sodium (USAN)
Refer to USAN for more details.

SUPPORTING DOCUMENTS:

Refer to Chemist's review #1 and #2.

REMARKS/COMMENTS:

The agency informed the applicant on October 30, 1990 by letter that the information submitted in response to the chemistry, manufacturing, and control deficiencies specified in the not approvable letter dated September 28, 1989 was evaluated and found to be acceptable. However, amendments have been sent in to address other issues posed in the not approvable letter dated October 30, 1990. The assigned chemist at this time developed some other requests when the amendments were submitted. This review addresses her concerns which was communicated to the applicant by telephone on May 16, 1994.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable for manufacturing and controls under section 505 of the Act pending the trademark consult and EER responses. An EER was issued on August 18, 1994. The assigned EER number is 6765. Its current status is pending. Refer to for more details. It should also be noted that the methods validation is still pending.

Janet G. Higgins 12/7/94

Janet G. Higgins
Reviewing Chemist

cc: Orig. NDA 19-931
HFD-540/Division File
HFD-540/Higgins
HFD-540/MO/Toombs
HFD-540/Pharm/Alam
HFD-540/Micro/Creedon
HFD-540/CSO/Turtil
HFD-540/SUPERVISOR/DeCamp 12/11/95
R/D Init by: SUPERVISOR
filename:**N19931.R03**

12/11/95

Consult #322 (HFD-540)

SULFACET CLEAR LOTION — Sodium Sulfacetamide Lotion 10%

The Committee is aware that USAN discourages the use of a proprietary name that incorporates the syllables of the USAN name since doing so may limit the availability of appropriate nonproprietary names to USAN. While we would normally express strong opposition to the proposed name because of its similarity to the USAN name, we recognize that Dermik is already marketing Sulfacet-R Lotion. In this case, we believe the Division reviewers should consider the appropriateness of pursuing this issue at this time. One factor to consider would be whether the Agency approved the name "Sulfacet-R Lotion." Please note that the approval status is being questioned since this product does not appear in the "Orange Book."

Other than the concern described above, the Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Ruth Mille, Chair 8/1/94

COMPLETED

COCK

Division of Anti-Infective Drug Products
Chemist's Review #2

NDA 19-931 August 28, 1990

Applicant: Dermik Laboratories
Ft. Washington, PA 19034

Proprietary Name: Sulfacet Clear Solution
Non-proprietary Name: sodium sulfacetamide

Initial Submission: 12/27/88

Amendments: 6/26/90

Remarks:

1. With regard to question #1 in the Chemist's Revew #1, dated 4/28/89, the firm has submitted the information. - Adequate
2. With regard to #2, the firm has submitted the information. - Adequate
3. With regard to #3, the firm has submitted the information. - Adequate
4. With regardd to #4, the firm has replied. - Adequate
5. With regard to #5, the firm has submitted the information. - Adequate
6. With regard to #6, the firm has submitted the information. - Adequate
7. With regard to #7, the firm has submitted the information. - Adequate
8. With regard to #8, the firm has submitted the information. - Adequate
9. With regard to question #9, the firm has submitted the information. - Adequate
10. With regard to question #10, the firm has submitted stability data. Adequate to support 24 months expiry date.
11. With regard to question #11, the firm has made commitment. - Adequate
12. With regard to question #12, the firm has submitted the information. - Adequate
13. With regard to question #13, the firm has responded favorably. - Adequate
14. With regard to question #14, the firm has submitted the information. - Adequate
15. With regard to question #15, the firm has responded favorably. - Adequate

Conclusions: The firm has adequately responded to all the questions raised in Chemist's Review #1, dated 4/29/90.

B Shetty 10/1/90

B. Vithal Shetty, Ph. D.
Chemist, HFD-520

cc: Orig: NDA 19-931
HFD-520
HFD-520/MO/DCBostwick
HFD-520/Pharm/REOsterberg
HFD-520/CSO/RCook
HFD-520/CHEM/BVShetty/th/10/1/90
R/D initialed by SUPVCHEM/9/27/90
n19931.rv2

10/2/90

Division of Anti-Infective Drug Products
Chemist's Review #1

NDA 19-931 April 28, 1989

Applicant:
Dermik Laboratories. Inc.
Ft. Washington. PA 19034

Contact:
James P. Thompson
(215)-956-5119

Proprietary Name:
Sulfacet Clear Lotion

Date of Submission:
December 27. 1988

Dosage Form / Route of Administration:
lotion / topical

Pharmacological Category / Principal Indication:
antibacterial / control of acne vulgaris

Structural Formula / Chemical Name:
sulfacetamide sod (USAN) $C_8H_9N_2NaO_3S.H_2O$

N-[(4-aminophenyl)sulfonyl]-acetamide, monosodium salt, monohydrate
m.w. 254.24
CAS 6209-17-2

Related NDA's, IND's and DMF's:

DMF
reference authorization provided
DMF manufacturing facilities, Rorer Pharmaceutical Corp.; Rorer is the parent company of the applicant; reference authorization provided
DMF
reference authorization provided
DMF
reference authorization provided
DMF , reference authorization provided
DMF
reference authorization provided
NDA 5-963.

NDA 19-525.

numerous ANDA's assigned to HFD-230

Remarks:

Sulfacetamide sodium is a compendial product. It is currently marketed as sterile ophthalmic ointments in 10% strength, and sterile ophthalmic solutions in 10 and 30% strength by Schering under NDA 5-963, as well as numerous other ANDA's. A lotion formulation of similar strength was the subject of NDA

The strength is stated on the basis of the anhydrous drug, rather than the hydrate, as is compendial practice.

Conclusions and Recommendations:

The application is not approvable under Section 505 of the Act. Specific items which are not approvable are identified under the following headings: Components and Composition, Raw Material Controls, Other Firms, Manufacturing and Processing, Laboratory Controls, Stability, Control Numbers, Samples and Results, Labeling, and Establishment Inspection. A draft of the chemist's portion of a not approvable letter is attached; CSO should draft the full letter.

The information obtained from DMF is incomplete. Specific deficiencies are identified under Synthesis. A draft letter requesting additional information be submitted to the DMF is attached.

Wilson H. De Camp, Ph.D.
Wilson H. De Camp, Ph. D.
Chemist, HFD-520

cc: Orig: NDA 19-931
HFD-100/Kumkumian
HFD-520
HFD-520/WHD
Init:ARCasola/
HFD-520/Powell
HFD-520/Joshi
HFD-520/Bostwick
WHD: 4/28/89

micro

Consultative Review to Division of Topical Drug Products (HFD-540)

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

Clinical Microbiological Labeling Review

NDA #:19-931 **REVIEW #**:2 **REVIEW DATE**: 10-FEB-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	22-DEC-88	23-DEC-88	12-MAY-94
AMENDMENTS	12-MAY-94	16-MAY-94	02-JUN-94
	26-AUG-94	29-AUG-94	29-AUG-94

Consult requested on: February 8, 1995 By: Mr. S. Turtil

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

CONTACT PERSON: Ronald F. Panner
Phone Number: (215)454-8000

DRUG PRODUCT NAME: Proprietary: Sulfacet
Nonproprietary: Sodium sulfacetamide
Chemical Type: sulfonamide Antibacterial
Therapeutic Class: 3 C

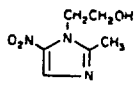
ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Topical Lotion
STRENGTHS: 10%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

N-[(4-aminophenyl)sulfonyl]acetamide, monohydrate, monosodium salt



Molecular Formula: $C_8H_9N_2NaSO_3.H_2O$
Molecular Weight: 254.24

SUPPORTING DOCUMENTS:
IND

REVIEW COMMENTS:

The following is the comment from this reviewer's last review (October 24, 1994): "The information in the clinical pharmacology subsection of the package insert may be misconstrued to suggest that the antibacterial activity of this compound is equivalent to an antimicrobial claim. Please suggest alternate wording that is more congruent with the function of the active compound, that is treatment versus prophylaxis."

The medical officer has suggested the following in her review dated November 28, 1994: "Microbiology: The sulfonamides are bacteriostatic agents. Sulfonamides inhibit bacterial synthesis of dihydrofolic acid by preventing the condensation of the pteridine with aminobenzoic acid through competitive inhibition of the enzyme dihydropteroate synthetase. Resistant strains have altered dihydropteroate synthetase with reduced affinity for sulfonamides or produce increased quantities of aminobenzoic acid."

The earlier comment from this reviewer apparently has not yet been relayed to the applicant. This reviewer has no objection to the suggested wording by the reviewing medical officer. However, the statement "Sodium sulfacetamide is a sulfonamide with antibacterial activity." in the description section is redundant and implies causality. This reviewer suggest truncating the sentence to read: "Sodium sulfacetamide is a sulfonamide."

Kathleen A. Creedon, Ph.D.
Review Microbiologist 2/10/95

cc:Orig. NDA 19-931
HFD-540/Division File
HFD-520/KCreedon/2-10-95
HFD-540/MO/EToombs
HFD-540/Pharm/SAlam
HFD-540/Chem/JHiggins
~~HFD-540/CSO/STurtil~~

Concurrence Only:
HFD-520/ActgDir/LGavrilovich
HFD-520/SUPERVISOR/ASheldon
R/D Init by: ATS;2/10/95
filename: **N19-931.rev**

Consultative Review to Division of
Topical Drug Products (HFD-540)

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

Clinical Microbiological Review

NDA #: 19-931 **REVIEW #:** 1 **REVIEW DATE:** 28-OCT-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	22-DEC-88	23-DEC-88	12-MAY-94
AMENDMENTS	12-MAY-94	16-MAY-94	02-JUN-94
	26-AUG-94	29-AUG-94	29-AUG-94

Consult requested on: May 30, 1994 By: Ms. R. Cook
(now assigned to Mr. S. Turtil)

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

CONTACT PERSON: Ronald F. Panner
Phone Number: (215)454-8000

DRUG PRODUCT NAME: Proprietary: Sulfacet
Nonproprietary: Sodium sulfacetamide
Chemical Type: sulfonamide Antibacterial
Therapeutic Class: 3 C

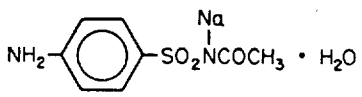
ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Topical Lotion
STRENGTHS: 10%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

N-[(4-aminophenyl)sulfonyl]acetamide, monohydrate, monosodium salt



Molecular Formula: $C_8H_9N_2NaSO_3.H_2O$
Molecular Weight: 254.24

SUPPORTING DOCUMENTS:

IND

INTRODUCTORY REMARKS:

This application is in response to a not approvable letter issued October 30, 1990, in which additional clinical trials were requested. A microbiology review of the manufacturing and controls had not been conducted on the original application.

REVIEW COMMENTS:

The product, Sulfacet Clear Lotion (10%) is a topical product to be sold in 2 oz. (59 mL) bottles. Methylparaben at % is used as the preservative, and a satisfactory preservative effectiveness has been submitted. The results of a microbial limits test was also submitted, however, the applicant has not submitted the corresponding standard operating procedure (SOP) for the microbial limits test.

The applicant has submitted a draft package insert based on the approved package insert for Sulfacet Acne Lotion (which contains 10% sodium sulfacetamide and 5% sulfur). Although the products do not have microbiologic claims for the treatment of acne vulgaris, the clinical pharmacology section states that the product works via its antimicrobial activity. The wording used is the same in all sulfacetamide products, and although is not the optimal wording, it is truthful in its content. Consequently, the first sentence of the clinical pharmacology subsection of the package insert may continue to read: "The most widely accepted mechanism of action of sulfonamides is the Woods-Fildes theory which is based on the fact that sulfonamides acta as competitive antagonists to para-aminobenzoic acid (PABA), an essential component for bacterial growth.

CONCLUSIONS & RECOMMENDATIONS:

This application is APPROVABLE from a microbiology perspective.

The following comments should be relayed to the applicant.

The standard operating procedure (SOP) for the microbial limits test should be submitted to complete the application record.

The information in the clinical pharmacology subsection of the package insert may be misconstrued to suggest that the antibacterial activity of this compound is equivalent to an antimicrobial claim. Please suggest alternate wording that is more congruent with the function of the active compound, that is treatment versus prophylaxis.

Kathleen A. Creedon 10/31/94

Kathleen A. Creedon, Ph.D.
Review Microbiologist 10/28/94

cc:Orig. NDA 19-931
HFD-540/Division File
HFD-520/KCreedon/10-28-94
HFD-540/MO/EToombs
HFD-540/Pharm/SAlam
HFD-540/Chem/JHiggins
HFD-540/CSO/STurtil 11/9/94

Concurrence Only:
HFD-520/ActgDir/LGavrilovich
HFD-520/SUPERVISOR/ASheldon
R/D Init by: ATS;10/31/94 11/3/94
filename: **N19-931.rev**

FDA Corres

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD and DRUG ADMINISTRATION
CENTER for DRUG EVALUATION and RESEARCH

Public Health Service

Memorandum

Date November 20, 1990

From Supervisory Pharmacologist, HFD-520

Subject NDA 19-931, Sulfacet Clear Lotion, 10%

To Ms. Rosemary Cook, CSO, HFD-520

In response to the request from our Division Director, Dr. M. M. Lumpkin (see attached), I have reviewed the pharmacology portion of the action packet for NDA 19-931 (Sulfacet Clear Lotion, 10%). Dr. Lumpkin expressed the opinion that the pharmacology rationale for approval was inadequate and requested a review to determine if animal data was needed to support approval of this NDA.

As a result, I examined the action packet and concluded that some specific animal-derived data would be appropriate to help support product approval and/or labeling statements to ensure safe handling and use of the product. The following data would be needed to satisfy the potential safety concerns that I believe are credible:

1- Ocular irritancy potential; data to be derived from a Draize eye irritation test using albino rabbits. Since the product can be used near the eyes, the potential for accidental eye exposure exists and appropriate warning statements would be needed if the product shows this capacity for injury.

2- Percutaneous penetration data regarding the sulfonamide. Dermal absorption data would be significant to the safety assessment if a portion of the patient population was allergic to sulfonamides because serious allergic responses could be provoked. Sulfonamides produce the second greatest number of allergic responses in humans in an arena where the penicillins are number one. Such data preferably could be obtained during a human clinical trial. If it is not possible to use humans, then an appropriate whole animal model could be used. The sponsor may also elect to use an in vitro model to determine the degree of percutaneous penetration or, perhaps, provide information from the biomedical literature to answer this question. The latter method must have provided the data using agency-acceptable protocols.

The sponsor should be informed about this data request as soon as possible so that delays in product approval will be minimal.

Robert E. Osterberg, Ph.D.

cc:
HFD-520 (Dr. Lumpkin)
HFD-520 (Mr. Bostwick) concur - D.C. Bostwick 11-28-90
HFD-520 (Pharmacology)

MMM 11/23/90

MEMORANDUM

DATE: 30 October 1990

TO: Robert Osterberg, Ph.D.

FROM: Murray M. Lumpkin, M.D.
Director, Division of Anti-infective Drug Products
HFD-520

SUBJECT: NDA-19931

Bob:

I received the action packet for NDA 19931 (Sulfacet Clear Lotion, 10%) today, and I am concerned that the Pharmacology review written by Mr. Davitt is inadequate in my opinion. The product is not approvable at this time because of clinical inadequacies, so I am going to sign the Non-approvable letter today. However, would you please review this section and determine whether animal data are needed for this product, and, if not, I think a memo to the NDA addressing that decision should be added. If animal data are needed, then we need to inform the sponsor of that decision as soon as possible.

Thanks.

cc: NDA-19931

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Telephone Memorandum

Date: December 15, 1994

To: Ms. Audrey Hackman

From: Janet G. Higgins
Review Chemist, HFD-540

Subject: NDA 19-931: Sulfacet® (Sodium Sulfacetamide 10%) Clear Lotion

Through: Wilson H. DeCamp, Ph.D.
Supervisory Chemist, DTDP, HFD-540 WD 1/11/95

Due to the changes that have been made to the NDA since its original submission in 1989, an updated methods validation package was requested. Ms. Hackman said she did not know when Dermik Laboratories would be able to submit the updated methods validation package, however, she would contact me by phone when she obtains a time frame from the chemists at Dermik Laboratories, Inc.

cc: Orig. NDA 19-931
HFD-540/ Higgins
HFD-540/ DeCamp
HFD-540/ Turtil
HFD-540/ Toombs
HFD-540/Alam
HFD-540/Creedon
HFD-540/Division File
filename: **N19-931.M01**

1/11/95

NDA 19-931

DEC 30 1988

Ronald F. Panner
Dermik Laboratories, Inc.
500 Virginia Drive
Fort Washington, PA. 19034

Dear Mr. Panner:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)/507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Sulfacet Clear Lotion (sodium sulfacetamide 10%)

Date of Application: December 22, 1988

Date of Receipt: December 23, 1988

Our Reference Number: NDA 19-931

Unless we find the application not acceptable for filing, the filing date will be February 23, 1989.

Please begin any communications concerning this applicaition by citing the NDA number listed above. Should you have any quesions concerning the NDA, please contact Mr. David Bostwick on (301) 443-0211.

Sincerely yours,

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA
HFD-82
HFD-710
HFD-220
HFD-500
HFD-520
HFD-520/LGavrilovich
HFD-520/MO
HFD-520/Chem
HFD-520/Pharm
HFD-520/DCBostwick:elp/12/29/88
4560m

12-29-88

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Date: September 26, 1989

To: Acting Director, Division of Anti-Infective Drug Products (HFD-520)

From: David C. Bostwick

Subject: NDA 19-931, Sulfacet (sodium sulfacetamide) Lotion, 10%.

I am forwarding the following information for your review:

1. Not Approvable letter
2. Medical Review - D.C. Bostwick and C.C. Evans, M.D.
3. Draft Statistical Review - B.K. Taneja, Ph.D.
4. Chemistry Review - W.H. DeCamp, Ph.D.
5. Pharmacology Review - J.M. Davitt
6. Draft Labeling

The active ingredient in this product is already used in many ophthalmic preparations.

The medical review finds that the application is not approvable because no physician global evaluation was done in the clinical studies. Although the statistical review in the package is in draft form, Dr. Nevius doesn't feel that the final version will be changed very much.

Chemistry is not approvable. The deficiences have been informally given to the sponsors, but we have not yet received any reply. Pharmacology is approvable. This application should be made not approvable.

David C. Bostwick
Chemist

cc: Orig NDA
HFD-82/HFD-520
HFD-520/DCBostwick:elp/09/26/89
HFD-520/WHDeCamp/HFD-520/CCEvans
HFD-520/JMDavitt
5111m

NDA 19-931

Mr. Ronald F. Panner
Director
Regulatory Affairs
Dermik Laboratories, Inc.
500 Virginia Drive
Fort Washington, PA 19034

JUL 23 1990

Dear Mr. Panner:

Reference is made to your New Drug Application (NDA) and to your amendment dated June 26, 1990, received by the Food and Drug Administration (FDA) on July 2, 1990, for Sulfacet Clear Lotion, 10%.

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 120 additional days will be required for its review.

The new due date is **October 30, 1990.**

If questions arise concerning this NDA, please contact Mr. Van C. Sickler, of the Project Management Staff, at (301) 443-6797.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
ORIG. NDA 19-931
HFD-520
HFD-520/DCBostwick BMB 7/23/90
HFD-520/CHEM/WDeCamp WDC 7/23/90
HFD-520/PHARM
HFD-521/PMS/VCSickler/sdj/7/20/90 VCS 7/23/90
F/T: 7/20/90

EXTENSION LETTER 2205u

MML 7/23/90

RECORD OF TELEPHONE CONVERSATION

DATE: May 16, 1994

TO: J. P. Thompson
of Dermik Laboratories, Inc.
Telephone Number (610) 454-3027

FROM: Rosemary Cook
of FDA
Telephone Number (301) 443-0257

SUBJECT: Recommendations from Team meeting

IND/NDA NUMBER: NDA 19-931

DRUG: Sulfacet Clear Lotion (sodium sulfacetamide lotion), 10%

SPONSOR/APPLICANT: Dermik Laboratories, Inc.

Mr. Thompson was informed of the following recommendations that were generated during the general team evaluation of NDA 19-931:

1. An updated listing of all applicable drug master files and manufacturing facilities should be submitted;

2. A statement, if applicable, that all chemistry, manufacturing, and controls information remains the same as of June 26, 1990 (date of the last submission referenced in the not approvable letter dated October 30, 1990) should be submitted. Otherwise, all revisions must be specified;

3. It should be confirmed whether SAS datasets for the clinical data included in the submission dated March 4, 1994, have been submitted;

4. Desk copies of the submission dated March 4, 1994 should be provided for review by the Pharmacologist and Chemist;

5. Draft labeling included in the submission dated March 4, 1994, should be revised to conform to the requirements of 21 CFR 201;

6. It should be confirmed whether a guinea pig sensitization study has been completed;

7. Copies of the study report, "In-Vitro Permeation of Sulfacetamide From a Clear Lotion Vehicle" should be submitted for review by the Biopharmaceutist and Chemist;

8. With regard to the microbiology review section, the following information should be included:

   A. Preservative effectiveness data; and

   B. Any microbiological quality controls associated with excipient testing and/or any sampling during the manufacturing process.

Mr. Thompson stated that a response to the recommendations would be submitted.

The conversation ended amicably.

cc:
Orig NDA 19-931
HFD-540
HFD-540/MO/Toombs
HFD-540/PHARM/Carlin
HFD-540/PHARM SUPV/Alam
HFD-540/CHEM/Rejali
HFD-540/CHEM SUPV/De Camp
HFD-520/MICRO SUPV/Sheldon
HFD-426/BIOPHARM/Ajayi
HFD-713/STAT SUPV/Harkins
HFD-540/PROJ MGR SUPV/Cook


Co. Corres

March 4, 1994

DERMIK LABORATORIES, INC.
Dedicated to Dermatology™
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 215-454-8000

DUPLICATE

A2

March 4, 1994

Lillian Gavrilovich, M.D., Acting Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Review II
Document Control Room #12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

AMENDMENT TO A PENDING APPLICATION

Dear Dr. Gavrilovich:

Reference is made to the following correspondence concerning Dermik Laboratories' NDA for Sulfacet® Clear (sodium sulfacetamide 10%) Lotion: our original NDA submission for Sulfacet® Clear Lotion dated December 22, 1988, your not approvable letter dated September 28, 1989, our subsequent communications dated October 25, 1989 and June 26, 1990, and specifically a second not approvable letter from Murray M. Lumpkin, M.D. dated October 30, 1990.

In addition to the above references, please also refer to the Background/ Overview of Clinical Investigations included in Volume 2.2 on page 25 of this submission, a copy of which is attached to this letter.

In Dr. Lumpkin's October 30, 1990 correspondence we were informed that our NDA was inadequate and therefore not approvable because "each clinical study did not include an acceptable physician global evaluation". With the exception of the previously mentioned inadequacy and final product labeling, we have been informed that all other information contained in the original NDA and related supplemental submissions has been evaluated and found to be acceptable.

Sections of the NDA application containing previously reviewed and evaluated information have not been resubmitted in this application, only those sections that were revised to include new information are resubmitted.

In response to the October 30, 1990 not approvable letter, Dermik Labs has conducted two additional controlled clinical studies that include global evaluations by the physicians who conducted the studies. The results of these studies are included in this submission.

Prior to completion of these clinical studies, CSO Ms. Rosemary Cook telephoned Dermik's Mr. James Thompson with additional requests from toxicologist Dr. Robert Osterberg. Dr. Osterberg requested that Dermik conduct a primary eye irritation study and a percutaneous absorption study with Sulfacet® Clear Lotion. Final reports for these studies are also included in this submission.

It is our belief that the data and information included in this amended application establish that Sulfacet® Clear Lotion is safe and effective in the treatment of acne vulgaris.

Sincerely yours,

Ronald F. Panner
Group Director
Regulatory Affairs

RFP/JPT/mab
Enclosures

BACKGROUND/OVERVIEW OF CLINICAL INVESTIGATIONS

Sodium sulfacetamide exerts an antibacterial effect against a wide range of gram negative and gram positive organisms. In addition to its use in the topical treatment of acne, it has been widely used to treat ophthalmic infections and seborrheic dermatitis. Sodium sulfacetamide has established a remarkable record of safety, and even very high aqueous concentrations are nonirritating to the delicate tissue of the eye. (Weinstein, L., "Sulfonamides." in The Pharmacological Basis of Therapeutics, 5 ed.; Goodman, L.A., and Gilman, A., eds.; Macmillan Publishing Co., Inc., 1975; 1119-1120).

While there are many testimonials attesting to the efficacy of sodium sulfacetamide in the treatment of acne vulgaris, there were no well-controlled studies confirming its efficacy. It was our intention to conduct controlled, double-blind studies that would confirm the efficacy of a topical sodium sulfacetamide 10% solution (Sulfacet® Clear) in the treatment of acne vulgaris.

The efficacy of Sulfacet® Clear Lotion was evaluated in two double-blind, randomized trials involving 107 patients with grade II or grade III acne (Study DO 1307).. After 10 weeks of treatment the 10% sodium sulfacetamide solution was significantly more effective than aqueous vehicle in the percent reduction of inflammatory lesions. Final reports for these studies were included in our original December 22, 1988 NDA submission.

Upon completion of the review of the previously mentioned clinical studies, Dermik Labs was informed by the Division of Anti-Infective Drug Products in an October 30, 1990 letter that the application was not approvable. The specific reason cited by the Division was that "each clinical study did not include an acceptable physician global evaluation."

As a result of this determination, Dermik Labs initiated two additional controlled clinical studies identical in design to the studies included in the original application, with the addition of the inclusion of a global evaluation by the physician. In one of these studies, the Parish study (Study DL-6013-9102), the global evaluations were made at the end of the investigation. In the other study, which was a multi-center study conducted by Drs. Berger and Maloney (DL-6013-9302), the global evaluations were made by the physicians at each follow-up visit and at the end of the study. Patient global evaluations were also made at the end of both studies.

After 10 weeks of treatment with Sulfacet® Clear Lotion the results of the two studies showed that inflammatory lesions were significantly reduced. More importantly, both the physician and patient global evaluations indicated significant improvement of patients treated with Sulfacet® Clear Lotion over vehicle.

Therefore, the results of these two additional controlled clinical studies should complete all outstanding requirements for approval.

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

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

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

NAME OF APPLICANT	DATE OF SUBMISSION
Dermik Laboratories, Inc.	March 4, 1994
ADDRESS *(Number, Street, City, State and Zip Code)* 500 Arcola Road Collegeville, PA 19426	TELEPHONE NO *(Include Area Code)* (610) 454-3026
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 19,931

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
sodium sulfacetamide	Sulfacet® Clear Lotion

CODE NAME *(If any)*	CHEMICAL NAME
SCL-10	Acetamide, N-[(4-aminophenyl) sulfonyl]-, mono-sodium salt, monohydrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Lotion	Topical	10%

PROPOSED INDICATIONS FOR USE

Sulfacet® Clear Lotion is indicated in the topical control of acne vulgaris

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314 420)* REFERRED TO IN THIS APPLICATION:

IND and see list of Drug Master Files in original application (Volume 1.1, page 2)

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

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

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

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☒ PRESUBMISSION ☐ ORIGINAL APPLICATION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

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

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

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

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

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ronald F. Panner Director, Regulatory Affairs	Ronald F. Panner	3/4/94
ADDRESS *(Street, City, State, Zip Code)*		**TELEPHONE NO.** *(Include Area Code)*
500 Arcola Road Collegeville, PA 19426		(610) 454-3026

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

NEW CORRESP
NC

DERMIK LABORATORIES, INC.
A RHÔNE-POULENC RORER COMPANY
Dedicated to Dermatology™

RCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

December 12, 1995

Jonathan K. Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Dermatologic and
Ophthamologic Drug Products
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

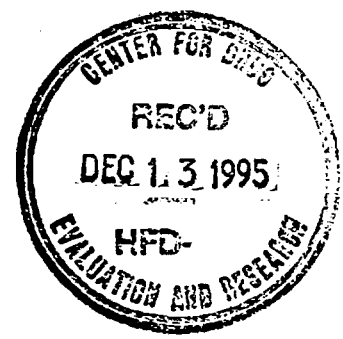
Reponse to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to a December 12, 1995 telephone conversation with members of your Project Management Staff during which Dermik was requested to submit patent information and a debarrment statement to our Sulfacet® Clear Lotion NDA. The following statements respond to this request:

As stated in Section 314.53(c)(3), Dermik Laboratories, Inc. believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1), we hereby certifiy that, in connection with this application, Dermik Laboratories, Inc. did not and will not use in any capacity the service of any person debarred under subsections 306(a) or (b) of the act.



If you have any questions or if I can provide you with any additional information, please contact me at (610) 454-3026.

Sincerely yours,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/JPT/man
Enclosure

EST 3/13/95

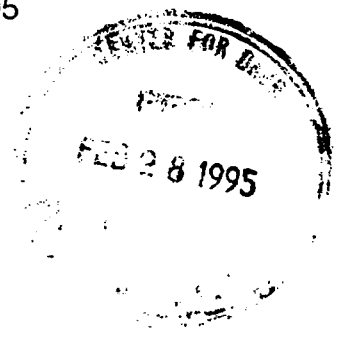
DERMIK LABORATORIES, INC.
Dedicated to Dermatology™
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

ORIGINAL

XR

February 27, 1995



Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD-540, Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to our NDA #19-931 for Sulfacet® Clear Lotion (sodium sulfacetamide 10%) and to Mr. Steven Turtil's February 21, 1995 telephone request that we provide certain additional information.

As requested, we are providing the following information.

Patent Information: There are no relevant patents relating to this product.

Marketing Exclusivity: In accordance with 21 CFR 314.108(b)(4), Dermik requests three years of marketing exclusivity for this product. Other applications for a different use (ophthalmic) have been approved for drugs containing the active moiety. This application (NDA #19-931) includes reports of new clinical investigations sponsored by the applicant that are essential to the approval of the application.

Debarment Certification: In accordance with subsection 306(k) of the Federal Food, Drug, and Cosmetic Act, Dermik certifies that we did not and will not use in any capacity the services of any person debarred under subsections 306(a) or 306(b) in connection with NDA #19-931.

Safety Update Review: According to 21 CFR 314.50(5)(vi)(a), the FDA requires that the applicant periodically update a pending application with any new safety information which may effect the product labeling. The original NDA was filed December 22, 1988. Two additional clinical trials were conducted at the Agency's request to support this application. The results of those trials were submitted as an amendment to the application on March 4, 1994. There has been no additional clinical experience with this product. Therefore, the application contains all of the currently known safety information relating to this product.

In addition, we are formally submitting a clarification of the component lauric-myristic 2:1 diethanolamide which has been the subject of several conversations with Dr. Janet Higgins, Reviewing Chemist.

This submission fully responds to all outstanding requests from the Agency regarding this application. If you have any further questions, please contact me at (610) 454-3026.

Sincerely yours,

Ronald F. Panner

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/alh/man
Enclosures

NEW CORRESP
NC

DERMIK LABORATORIES, INC.
A RHÔNE-POULENC RORER COMPANY
Dedicated to Dermatology™

RCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

December 12, 1995

Jonathan K. Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Dermatologic and
Ophthamologic Drug Products
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Reponse to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to a December 12, 1995 telephone conversation with members of your Project Management Staff during which Dermik was requested to submit patent information and a debarrment statement to our Sulfacet® Clear Lotion NDA. The following statements respond to this request:

As stated in Section 314.53(c)(3), Dermik Laboratories, Inc. believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1), we hereby certifiy that, in connection with this application, Dermik Laboratories, Inc. did not and will not use in any capacity the service of any person debarred under subsections 306(a) or (b) of the act.

If you have any questions or if I can provide you with any additional information, please contact me at (610) 454-3026.

Sincerely yours,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/JPT/man
Enclosure

DERMIK LABORATORIES, INC.
A RHÔNE-POULENC RORER COMPANY
Dedicated to Dermatology™

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

July 3, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA 19-931
Klaron® Lotion 10%
(sodium sulfacetamide lotion, 10%)

Amendment to a Pending Application
- Response to Approvable Letter

Dear Dr. Wilkin,

Reference is made to your June 19, 1996 letter indicating that Dermik's NDA for Sulfacet Clear Lotion (sodium sulfacetamide lotion, 10%) is approvable and to our June 24, 1996 letter informing you that Dermik intended to amend this application and respond to your June 19, 1996 letter. This submission constitutes that response.

Included in this submission are specific responses to each of the requests made in the approvable letter . Please note that Dermik has selected a new trade name (Klaron® Lotion) for this product.

We believe this submission fully responds to all of your requests. If you have any questions regarding this submission, please contact me at (610) 454-3026.

Sincerely,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/alh/man
Encloures

DERMIK LABORATORIES, INC.

FORT WASHINGTON, PENNSYLVANIA 19034 215-628-6529

ORIG

DEC - 8 1988

December 22, 1988

DEC 23 1988

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
HFD 520
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Original New Drug Application
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Dear Dr. Gavrilovich:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and in accordance with the requirements of 21 CFR 314 Dermik Laboratories, Inc. is submitting an Original New Drug Application for Sulfacet® Clear (sodium sulfacetamide 10%) Lotion.

Sodium sulfacetamide is a sulfonamide with antibacterial activity. This application contains data and information that confirm the safety and efficacy of sodium sulfacetamide in the topical treatment of acne. In addition to its use in the treatment of acne vulgaris, sodium sulfacetamide has been widely used to treat ophthalmic infections and seborrheic dermatitis for over forty years.

In accordance with 21 CFR 314.50, this application contains the following technical sections: (1) Chemistry, Manufacturing and Controls, (5) Clinical Data and (6) Statistical (identical in content to the clinical section). Copies of the case report forms for the adequate and well controlled clinical studies upon which the efficacy of Sulfacet® Clear Lotion is based are also included in this application.

Three copies of the Methods Validation package and labeling required by 21 CFR 314.50(e) are included in the review copy of this application. One copy is included in the archival copy.

Dermik Laboratories, Inc. considers the information in this application to be confidential and proprietary and we request that no portions thereof be disclosed to third parties, under FOI or otherwise, without prior discussion with us.

Should you have any questions or require any additional information during the review of this application, please contact me at (215) 956-5119.

Sincerely yours,

James P. Thompson /for

Ronald F. Panner
Director
Regulatory Affairs

RFP/get

Enclosures

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

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31, 1989.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
23DEC88	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
520	19-931

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

NAME OF APPLICANT	DATE OF SUBMISSION
Dermik Laboratories, Inc.	12/22/88
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
500 Virginia Drive Fort Washington, PA 19034	(215) 283-0200
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
sodium sulfacetamide	Sulfacet® Clear Lotion

CODE NAME *(If any)*	CHEMICAL NAME
SCL-10	Acetamide, N-[(4-aminophenyl) sulfonyl]-, mono-sodium salt, monohydrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Lotion	Topical	10%

ROPOSED INDICATIONS FOR USE

Sulfacet® clear Lotion is indicated in the topical control of acne vulgaris

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

See attached list of Drug Master Files.

RECEIVED
CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 23 1988

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

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

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

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

PRESUBMISSION
☒ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

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

FORM FDA 356h (3/87)

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
1. Index	X
2. Summary (21 CFR 314.50 (c))	X
3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))	X
4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)	
b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))	X
c. Labeling (21 CFR 314.50 (e) (2) (ii))	
i. draft labeling *(4 copies)*	X
ii. final printed labeling (12 copies)	
5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))	X
6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))	
7. Microbiology section (21 CFR 314.50 (d) (4))	
8. Clinical data section (21 CFR 314.50 (d) (5))	X
9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))	
10. Statistical section (21 CFR 314.50 (d) (6))	X
11. Case report tabulations (21 CFR 314.50 (f) (1))	X
12. Case reports forms (21 CFR 314.50 (f) (1))	X
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
15. OTHER *(Specify)*	

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

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

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ronald F. Panner Director, Regulatory Affairs	James P. Thompson /for	12/22/88

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
500 Virginia Drive Fort Washington, PA 19034	(215) 956-5119

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

☆ U.S GOVERNMENT PRINTING OFFICE:1987-181-338/55255

DERMIK LABORATORIES, INC.

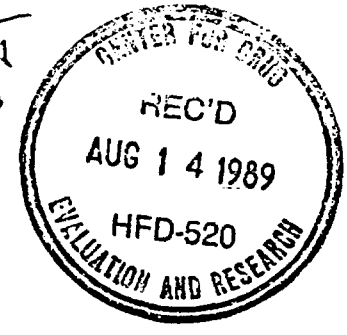
500 VIRGINIA DRIVE • FORT WASHINGTON, PENNSYLVANIA 19034

ORIG

NDA ORIG AMENDMENT
(BM)

August 8, 1989

8-16-89



Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Review II
Center for Drug Evaluation and Research
HFD 520
Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide)

Dear Dr. Gavrilovich:

Attached is our reply to Mr. David Bostwick's July 27, 1989 telephone questions concerning our NDA for Sulfacet® Clear Lotion.

Please contact us if additional information is required.

Sincerely yours,

James P Thompson/for

Ronald F. Panner
Director
Regulatory Affairs

RFP/get

Enclosure

DERMIK LABORATORIES, INC.

920A HARVEST DRIVE, SUITE 200, BLUE BELL, PA 19422 215-540-8300/FAX: 215-540-8320

ORIG.NEW CORRES.

ORIG

October 5, 1989

10-17-89

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Review II
Center for Drug Evaluation and Research
HFD 520
Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Dear. Dr. Gavrilovich:

Reference is made to your September 28, 1989 letter which indicates that our New Drug Application for Sulfacet® Clear Lotion is not approvable.

As required under 21 CFR 314.120 the purpose of this communication is to inform you of our intent to file an amendment to this application.

CENTER FOR DRUG
REC'D
OCT 12 1989
HFD-520
EVALUATION AND RESEARCH

Sincerely yours,

Judith R. Plon

Judith R. Plon
Associate Director
Regulatory Affairs

JRP/get

DERMIK LABORATORIES, INC.
500 VIRGINIA DRIVE, FORT WASHINGTON, PA 19034

OPTS

June 26, 1990

Murray Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Review II
Center for Drug Evaluation and Research
HFD 520
Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion, 10%
(sodium sulfacetamide)

AMENDMENT TO PENDING APPLICATION

Dear. Dr. Lumpkin:

Reference is made to the Agency's September 28, 1989 letter informing us that our pending New Drug Application for Sulfacet® Clear (sodium sulfacetamide) Lotion 10% is not approvable. Specifically, we were informed that our application was not approvable because the adequate and well controlled clinical efficacy studies which demonstrated a statistically significant superiority of Sulfacet Clear® Lotion over vehicle, did not include subjective global evaluations by the physicians. The letter also delineated the deficiencies in the manufacturing and control information that was submitted in support of our application.

This submission contains data and information that responds to all Agency comments and/or questions concerning our pending Sulfacet® Clear Lotion application. Included in this amendment are the overall clinical evaluations of the investigators who conducted the Sulfacet® Clear Lotion controlled efficacy trials. Also included in this amendment is manufacturing and control information that corrects the inadequacies in our pending application.

Sincerely yours,

Ronald F. Panner

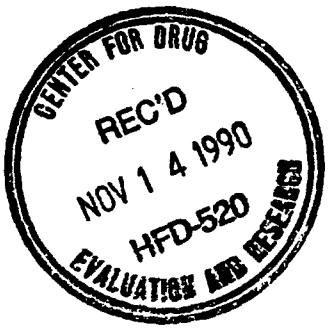
Ronald F. Panner
Director
Regulatory Affairs

RFP/get

Enclosures

DERMIK LABORATORIES, INC.
500 VIRGINIA DRIVE, FORT WASHINGTON, PA 19034

ORIG NEW CORRES



November 8, 1990

11-27-90

Murray Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Review II
Center for Drug Evaluation and Research
HFD 520
Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Dear Dr. Lumpkin:

Reference is made to your October 30, 1990 letter which indicates that our New Drug Application for Sulfacet® Clear Lotion is not approvable.

As required under 21 CFR 314.120 the purpose of this communication is to inform you of our intent to file an amendment to this application.

Sincerely yours,

Ronald F. Panner
Director
Regulatory Affairs

RFP/get

DERMIK LABORATORIES, INC.

500 VIRGINIA DRIVE • FORT WASHINGTON, PENNSYLVANIA 19034

ORIG

New Copies

January 25, 1991

Murray Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Review II
Center for Drug Evaluation and Research
HFD 520
Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

2-8-91

NDA 19-931
Sulfacet® Clear Lotion, 10%
(sodium sulfacetaide)

Dear Dr. Lumpkin:

Reference is made to your October 30, 1990 letter informing us that our New Drug Application for Sulfacet Clear Lotion was not approvable. Reference is also made to our November 8, 1990 letter informing you of our intent to file an amendment to this application which has kept our application active.

The purpose of this letter is to request a meeting to discuss the current status of the application and our future plans. The following dates for the meeting are acceptable to us: February 2, 5 & 28, and March 1, 5, 7 & 8, 1991. We would prefer a morning meeting.

The Dermik representatives who will be present at the meeting are:

Albert M. Packman, D.Sc., Vice President and Technical Director
Ronald F. Panner, Director, Regulatory Affairs
James P. Thompson, Senior Associate, Regulatory Affairs

We will contact your Division shortly to determine if any of our proposed meeting dates are acceptable.

Sincerely yours,

James P. Thompson /for

Ronald F. Panner -
Director
Regulatory Affairs

RFP/man

-91
4-91

DERMIK LABORATORIES, INC.

500 VIRGINIA DRIVE • FORT WASHINGTON, PENNSYLVANIA 19034

ORIG

March 22, 1991

Murray Lumpkin, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520

Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion, 10%
(sodium sulfacetamide)

AMENDMENT TO PENDING APPLICATION

Dear Dr. Lumpkin:

Reference is made to your October 30, 1990 letter informing us that our New Drug Application for Sulfacet® Clear (sodium sulfacetamide) Lotion, 10% was not approvable because our controlled clinical studies did not include a physician global evaluation. Reference is also made to our November 8, 1990 letter informing you of our intent to file an amendment to this application as required by 21 CFR 314.120.

Included in this submission is an outline of a proposed clinical study that we believe will provide additional confirmation of the statistically significant efficacy results demonstrated in the controlled clinical studies previously submitted to our Sulfacet Clear Lotion NDA. After you have had an opportunity to review this outline, we would like to meet with you briefly and/or appropriate members of your staff to discuss the details of this study prior to its finalization.

If you have any questions, please call me at 215-956-5119.

Sincerely yours,

Judith R. Plan for

Ronald F. Panner
Director
Regulatory Affairs

RFP/man

Dedicated to Dermatology

DERMIK LABORATORIES, INC.

FORT WASHINGTON, PENNSYLVANIA 19034

ORIG New Copies

No Reply MB 4.23.91

April 9, 1991

Murray M. Lumpkin, M. D., Director
Division of Anti-Infective Drug Products
Office of Drug Review II
Center for Drug Evaluation and Research, HFD 520
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

19-931

RE: Sulfacet® Clear Lotion, NDA ~~19-031~~

General Correspondence

Dear Dr. Lumpkin:

This letter will serve to inform you that during the period 14 March 1991 to 19 March 1991, Investigators from the Philadelphia District Office of FDA conducted an NDA pre-approval inspection for Sulfacet® Clear Lotion, NDA 19-031.

At the conclusion of the inspection, an FDA 483 was issued listing four Observations made during the Investigation. Response to the FDA 483 was made in a 28 March 1991 letter to Loren Y. Johnson, District Director, a copy of which is included with this letter for your information.

Of special interest to your Division is the commitment made as part of our Response to Observation 1 of the FDA 483 in which we indicate that an additional stability report will be submitted to this application by 31 July 1991.

Dermik Laboratories Inc. and Rhône-Poulenc Rorer, Inc., the parent company of Dermik, have requested facility approval from the District Office due to the fact that the FDA 483 did not address any GMP violations associated with the Dermik operation.

If I can be of further assistance, please contact me.

Sincerely,

Margaret S. Masters
Associate Director, Regulatory Control

MSM/mag
Attachment

Desk Copy: Dr. B. V. Shetty

605H

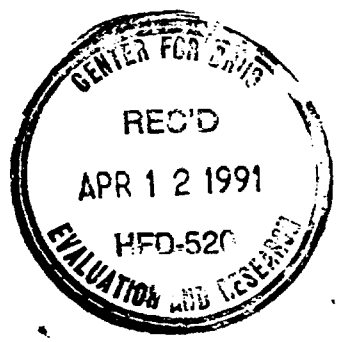
RHÔNE-POULENC RORER

RHÔNE-POULENC RORER INC.

500 VIRGINIA DRIVE
FORT WASHINGTON, PA 19034
TEL 215-628-6800

Registered Mail
Return Receipt Requested

March 28, 1991



Mr. Loren Y. Johnson
District Director
Department of Health and Human Services
Food and Drug Administration
900 U.S. Custom House
2nd and Chestnut Streets
Philadelphia, PA 19106

Dear Mr. Johnson:

During the period 14 March 1991 to 19 March 1991 an NDA pre-approval inspection for Sulfacet Clear Lotion was conducted by Investigators, Joan A. Loreng and Rita F. La Rocca. The following are the FD 483 observations made by the inspectors and our formal responses:

1. Stability samples of Sulfacet Clear Lotion exhibited a progressive darkening upon aging. No conclusion has been drawn as to the cause or significance of the color change.

Response

Proposed specifications for product color do allow for some color change (i.e. colorless translucent to amber-grey). A full stability report, including information on the cause and significance of the product color change upon aging, will be provided to the FDA Reviewing Chemist, Dr. B. V. Shetty, by 31 July 1991.

2. Sulfanilamide, a known degradation product of Sulfacet Clear Lotion, is not mentioned in the assay method. The peak became apparent in the HPLC chromatogram as early as six months.

Response

The assay method was developed in a manner to ensure that known degradation products, including sulfanilamide, were properly separated on the HPLC chromatogram. Changes will be incorporated in the assay method to ensure that sulfanilamide is identified and properly quantitated for purposes of stability testing.

3. Records of analysis of sulfacetamide raw material used in batches of Sulfacet Clear Lotion manufactured for clinical trials were not retained.

Response

The clinical batches referenced in the FD 483 were manufactured in 1983. Our written policy for maintaining raw material analytical release records states that they will be held on file for seven years and then destroyed. This policy was followed for the raw materials in question.

We agree to change our procedures to ensure that pertinent raw material control records are maintained as part of the clinical batch record file. This will ensure that all necessary information is maintained and available for review.

4. The density of pilot batch Sulfacet Clear Lotion, Lot # CLR 7-32, was not determined at the time of manufacture. The determination is required for conversion of weight/weight potency to weight/volume potency. The product is labeled per weight/volume basis.

Response

The current assay method for Sulfacet Clear (2S-120-8) states that values should be converted to w/v % by multiplying w/w % by density. The omission of the density test for Lot # CLR 7-32 was an oversight. Assay results for release of Sulfacet Clear Lotion will continue to be converted to w/v % through individual density determinations.

For purposes of stability, calculations of assay results will be w/w % in order to reduce variation associated with density calculations (caused by entrapped air in viscous lotion). The product specification will be converted from w/v % to w/w % by utilizing a standard density value calculated from a grand mean of multiple determinations.

In view of the fact that facility GMP violations are not at issue with respect to this inspection and that Rhône-Poulenc Rorer commits to provide an updated stability information report and method to the reviewing chemist for this New Drug Application, we request that facility approval not be withheld. Further, Dermik Laboratories and Rhône-Poulenc Rorer, Inc. commit to full validation of the product process prior to introduction of the marketed product.

Please do not hesitate to contact me if there are any unresolved issues with respect to this inspection.

Sincerely,

Charles F. Boudreau
Director, Quality Control

CFB/cc

cc: W. S. Hitchings, Ph.D., Vice President, Q.A.
J. A. Loreng, Investigator, FDA
M. M. Lumpkin, M.D., Director, Division of Anti-Infective Drug Products, FDA
B. V. Shetty, Ph.D., Reviewing Chemist
R. H. Thurman, President, Rhône-Poulenc Rorer Pharmaceutical Corporation

[redacted]
DERMIK LABORATORIES, INC.
500 VIRGINIA DRIVE, FORT WASHINGTON, PA 19034
Phone: (215) 628-6000

ORIG NEW CORRES

OR

October 15, 1991

Murray Lumpkin, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room #12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

11-1-91

NDA 19-931
Sulfacet® Clear Lotion, 10%
(sodium sulfacetamide)

CHANGE OF ADDRESS

Dear Dr. Lumpkin:

Effective November 7, 1991, Dermik Laboratories, Inc. is relocating to our new worldwide corporate headquarters. Our new address, telephone and FAX numbers are:

Dermik Laboratories, Inc.
Regulatory Affairs, H10
500 Arcola Road
Collegeville, PA 19426

Phone: (215) 454-3026
FAX: (215) 454-5287

Please direct all future correspondence concerning this application accordingly.

Sincerely yours,

Donald F. Dwyer for

Ronald F. Panner
Director
Regulatory Affairs

RFP/ild

Encl.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 24 1991
HFD-520

Dedicated to Dermatology

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

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

(Title 21, Code of Federal Regulations, 314)

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

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. A

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

NAME OF APPLICANT	DATE OF SUBMISSION
DERMIK LABORATORIES, INC.	October 15, 1991
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
500 Virginia Drive Fort Washington, PA 19034	(215) 956-5119
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	19-931

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
sodium sulfacetamide	Sulfacet Clear Lotion

CODE NAME *(If any)*	CHEMICAL NAME
SCL-10	Acetamide, N-[(4-aminophenyl) sulfonyl], mono-sodium salt, monohydrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Lotion	Topical	10%

PROPOSED INDICATIONS FOR USE

Topical control of Acne vulgaris.

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

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

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

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

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

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

PROPOSED MARKETING STATUS *(Check one)*

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

RHÔNE-POULENC RORER

DUPLICATE

RHÔNE-POULENC RORER CENTRAL RESEARCH
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107

RONALD F. PANNER
GROUP DIRECTOR
WORLDWIDE REGULATORY AFFAIRS OPERATIONS
TEL. 610-454-3026
FAX: 610-454-5299

May 12, 1994

Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to our April 19, 1994 telephone conversation with Ms. Rosemary Cook in which she requested we submit information to the Microbiology and Pharmacokinetics / Bioavailability sections of our NDA for Sulfacet® Clear (sodium sulfacetamide) Lotion 10%. Reference is also made to our May 11, 1994 telephone conversation with Ms. Cook in which she further clarified the information needed to satify the Microbiology request. This submission specifically responds to the Microbiology request. Information in support of a waiver for in vivo bioavailability studies is being sent under a separate cover.

In our original NDA application, we provided background information on sodium sulfacetamide which indicated that this drug has historically been used as an antibacterial agent. However, in this NDA we do not make microbiologic claims relating to the use of this drug for the treatment of acne vulgaris. Primary acne is not considered a bacteriologic condition. Our clinical protocols were not designed to investigate the antibacterial activities of Sulfacet® Clear. Our clinical studies indicate that the beneficial effects of Sulfacet® Clear for the treatment of acne are primarily due to anti-inflammatory actions.

The regulations in 21 CFR 314.50(d)(4) requires submission of a Microbiology section if the drug is an anti-infective agent. Although we are not claiming antimicrobial activity in this NDA, at Ms. Cook's request, we have included in this submission to our NDA the following information to be provided to the Microbiology reviewer:

Item 1. Dermik Formulary procedure number 3M-510-01: Preservative Effectiveness - USP Method (previously submitted as pages 116-117 of the original NDA)

Item 2. Sulfacet® Clear test results for above method (previously submitted as page 118 of the original NDA) and a statement interpreting these results

Item 3. Results of Microbiological Analysis of two clinical lots of Sulfacet® Clear using Dermik method number 3M-501

Item 4. A copy of the NDA summary (Volume 1) included in the original NDA submission

Item 5. A copy of the updated NDA summary (Volume 2.1) included in the NDA amendment submitted March 4, 1994

We expect that this information will be useful in your evaluation of our NDA. If you have any questions, please contact me at (610)454-3026.

Sincerely,

Kathryn A. Roberts for

Ronald F. Panner
Group Director
Worldwide Regulatory
Affairs Operations

RFP/ALH/man
Enclosures

DERMIK LABORATORIES, INC.
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EL. 215-454-8000

AB

DUPLICATE

May 13, 1994

Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD-540 Room 12B45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

19-931
NDA 19-93X
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request
for Information

Request For a Waiver of In-Vivo
Bioavailability Studies

Dear Dr. Wilkin:

Reference is made to our April 19, 1994 telephone conversation with Ms. Rosemary Cook, Acting Supervisor in which she requested we submit information to the Pharmacokinetics / Bioavailability and Microbiology sections of our NDA for Sulfacet® Clear Lotion (sodium sulfacetamide 10%). Reference is also made to our subsequent telephone conversation of April 26, 1994 with Dr. Francis Pelsor of the Biopharmaceutics Division in which we discussed the applicability of a waiver for in vivo bioavailability studies for the same product. This submission specifically responds to the Pharmacokinetics / Bioavailability request. Information to be submitted to the Microbiology section is being provided under a separate cover.

With this letter, we are requesting a waiver of in vivo bioavailability based upon 21 CFR 320.22 (b)(3)(i) which indicates a waiver is applicable to a drug product for which the bioavailability is considered self-evident because the drug is a solution for application to the skin. Attached please find the following information, supportive of our request for a waiver:

Item 1. The study report for a percutaneous absorption study titled "In Vitro Permeation of Sulfacetamide from a Clear Lotion Vehicle" by Thomas J. Franz and Paul A. Lehman, previously submitted to section (d) V. F. in the NDA amendment of March 4, 1994 (Vol. 2.4, pages 69-107),

Item 2. The Pharmacological Basis of Therapeutics, Third edition by Goodman and Gilman, page 1160 which lists the average concentration of sulfacetamide after oral administration, and an evaluation of how those levels compare with what we might expect based on our in vitro data,

Item 3. A statement confirming that the formulations used in the clinical studies and the percutaneous absorption study are the same as the formulation intended to be marketed,

Item 4. Results of a literature search (1966 to present) of the adverse reactions associated with topical administration of sodium sulfacetamide and a comparison of these reactions with those observed in the Clinical studies submitted in our NDA.

Item 5. The Medical Literature review summary included in the original NDA submission (Volume 1.5, pages 231-248)

Item 6. The Integrated Summary of Safety Information included in the NDA amendment of March 4, 1994 (Volume 2.4, pages 119-129)

Item 7. A copy of the NDA summary (Volume 1) included in the original NDA submission

Item 8. A copy of the updated NDA summary (Volume 2.1) included in the NDA amendment submitted March 4, 1994

We believe this information supports our request for a waiver of in vivo bioavailability studies for Sulfacet® Clear Lotion (sodium sulfacetamide 10%). If you have any questions, please contact me at (610)454-3026.

Sincerely,

Ronald F. Panner
Group Director
Worldwide Regulatory
Affairs Operations

RFP/ALH/ccr

RHÔNE-POULENC RORER

DUPLICATE

RHÔNE-POULENC RORER CENTRAL RESEARCH
500 ARCOLA ROAD
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COLLEGEVILLE, PA 19426-0107

RONALD F. PANNER
GROUP DIRECTOR
WORLDWIDE REGULATORY AFFAIRS OPERATIONS
TEL. 610-454-3026
FAX: 610-454-5299

June 24, 1994

Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD 540, Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Dear Dr. Wilkin:

Reference is made to a June 20, 1994 letter concerning Sulfacet Clear (sodium sulfacetamide 10%) Lotion which we received from Dr. Funmilayo O. Ajayi as a facsimile transmission June 21, 1994.

This submission contains information from the NDA for Sulfacet Clear Lotion that was requested by Dr. Ajayi in her letter.

If you have any questions concerning the information included in this submission or would like us to provide any additional information, please contact me at (610) 454-3026.

Sincerely yours,

James R. Thompson/for

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

Desk Copy: Funmilayo O. Ajayi, Ph.D.

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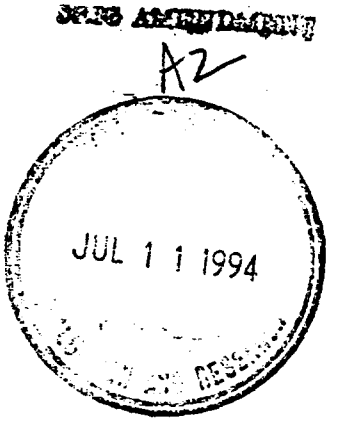
DUPLICATE

July 01, 1994



Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD-540, Room 12B45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA #19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA
Request for Information

Amendment to a
Pending Application

Dear Dr. Wilkin,

Reference is made to our NDA #19-931 for Sulfacet® Clear Lotion (sodium sulfacetamide, 10%) and to our telephone conversation with Ms. Rosemary Cook, CSO, on 16-May-1994 in which she requested updated and/or additional information regarding this NDA. Reference is also made to our telephone conversation with Dr. Nahid Rejali, Reviewing Chemist, on 16-May-1994 in which she relayed two CMC questions. These FDA comments and Dermik's responses are attached along with any additional supporting information.

We believe this submission fully responds to any outstanding comments in reference to this NDA. If you have any further comments, please contact me at (610)454-3026.

Sincerely Yours,

James P. Thompson/for

Ronald F. Panner
Group Director
Worldwide Regulatory
Affairs Operations

Dermik Responses to FDA Comments on the following:

CMC Information

Labeling

Nonclinical Pharmacology and Toxicology

Human Pharmacokinetics and Bioavailability

Microbiology

Statistics

CMC Information

FDA Comment: The application should be updated to include recent references to all Drug Master Files.

Dermik Response: The following DMFs included in the original NDA (Volume 2; pages 6, 52, 53, 54, and 55, respectively) have been updated and were directly submitted to the FDA by the providers. Copies of each of the updated DMF letters are included in this submission as Attachment 1:

The DMF for Rorer Pharmaceutical Corp. included in the original NDA (Volume 2, page 45) is no longer applicable. According to 21 CFR 314.420, the DMF is replaced by the pre-approval inspection for a U.S. manufacturing site.

FDA Comment: The names and addresses of all manufacturing and packaging facilities should be updated or if they are the same, a statement to that effect should be made.

Dermik Response: With respect to the manufacturing and packaging facilities, the information currently included in the NDA is correct.

FDA Comment: Are the manufacturing and packaging facilities identified in the NDA ready for an inspection?

Dermik Response: As discussed with Dr. Rejali during a telephone conversation on 30-Jun-1994, these facilities are prepared for another pre-approval inspection.

FDA Comment: Have any of the previously manufactured lots of Sulfacet® Clear been validated?

Dermik Response: None of the previously manufactured lots of Sulfacet® Clear have been validated. Protocols for the validation of the manufacturing process have been generated. The first production lot and two subsequent lots will be validated utilizing these protocols.

FDA Comment: Dermik should provide a statement that the CMC information is the same as it was in the original application and the CMC amendment submitted 26-Jun-1990. If it is not the same, revisions should be identified.

Dermik Response: In response to specific requests from Dr. Funmilayo Ajayi, Biopharmaceutist, and Dr. Nahid Rejali, Chemist, we have attached a copy of the updated stability data (Attachment 2) that were previously submitted in our 26-Jun-1990 and 24-Jun-1994 amendments.

During our review of the CMC information, we discovered that was incorrectly listed as an ingredient throughout the original NDA (Volume 1, page 18 and Volume 1.2, pages 10, 12, 13, 36, 37, 40, 42, and 44). Likewise, the 26-Jun-1990 CMC amendment references the incorrect ingredient in response to Comment 12.B. and in Attachments I, III, and VI and Appendix II. The correct name for this component is

Please be advised that has never been a component of Sulfacet® Clear Lotion (sodium sulfacetamide 10%). The NDA documentation is the only place where this error occurred. All laboratory and batch records throughout development and stability test batches and the final Master Formula correctly list as a component in Sulfacet® Clear Lotion.

Attachment 3 of this submission includes two items addressing this issue: 1) a copy of the analytical report form for and 2) Dermik Formulary DF 07-0066-0128: Sulfacet Clear Lotion which correctly lists as an ingredient in Part III of both the formula card and the manufacturing directions.

Comment 12.B. in your 28-Jun-1989 letter to Dermik stated, "12. The labels and labeling are inadequate to insure the safe and effective use of the drug as follows: B. the NF name must be used." In our 26-Jun-1990 response to this comment, we incorrectly agreed to your requested change. However, in order to accurately identify the ingredient, the correct name will be used in the final printed labeling for this product.

The current CMC information for this application is the same as the CMC information included in the original application and the 26-Jun-1990 CMC amendment with the exception of the incorrect ingredient name as described above.

FDA Comment: Provide copies of the permeation study included in the 04-Mar-1994 amendment for the Chemistry reviewer.

Dermik Response: A copy of this study report is being included in this submission as Attachment 4.

FDA Comment: Submit a separate desk copy of the CMC section that was included in the 04-Mar-1994 amendment.

Dermik Response: A copy of the CMC section that was included in the 04-Mar-1994 amendment is included in this submission as Attachment 5.

Labeling

FDA Comment: The labeling included in the 04-Mar-1994 submission should be reviewed and revised appropriately to be in compliance with 21 CFR 201. Ms. Cook said that we should make sure the general sulfonamide warning re: sensitivity is included in the labeling.

Dermik Response: We have reviewed the labeling included in the 04-Mar-1994 submission. This labeling is in compliance with 21 CFR 201 and includes the general sulfonamide warning regarding hypersensitivity.

As mentioned in our CMC response, the labeling will be revised to replace

Nonclinical Pharmacology and Toxicology

FDA Comment: Submit a separate desk copy of the Pharmacology / Toxicology section that was included in the 04-Mar-1994 amendment.

Dermik Response: A copy of the Pharmacology / Toxicology section that was included in the 04-Mar-1994 amendment is included in this submission as Attachment 6.

Human Pharmacokinetics and Bioavailability

FDA Comment: Provide copies of the permeation study included in the 04-Mar-1994 amendment for the Biopharmaceutist.

Dermik Response: A copy of the permeation study was included in our 13-May-1994 Pharmacokinetics / Bioavailability amendment. An additional copy is being included in this submission as Attachment 4.

Microbiology

FDA Comment: Provide additional preservative effectiveness information if available. Additionally, provide any microbiological quality control information generated during the manufacturing process. Excipient testing should be included.

Dermik Response: Our 12-May-1994 Microbiology amendment completely responded to this request.

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ORIGINAL

September 9, 1994

Ella Toombs, M.D.,
Medical Reviewer
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD-540, Room 17B45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA #19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA
Request for Information

Dear Dr. Toombs,

Reference is made to our NDA #19-931 for Sulfacet® Clear Lotion (sodium sulfacetamide, 10%) and to your request that we submit a disk containing the Clinical Section of this NDA in Word Perfect.

Enclosed, please find a disk containing the Word Perfect study reports and tables for the Berger, Maloney, and Parish studies as well as the ASCII files for the tables. The Word Perfect files are compatible with Word Perfect Version 5.1. Also included in this submission is a letter from our statistical consultant which lists the file name, type, and content.

We expect that this information will assist you in your review of this NDA. If you have any further questions, please contact me at (610)454-3026.

Sincerely Yours,

James P. Thompson for

Ronald F. Panner
Group Director
Worldwide Regulatory
Affairs Operations

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Quad

BZ

September 23, 1994

Jonathan Wilkin, M.D., Director
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5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

AMENDMENT TO A PENDING APPLICATION

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Wilkin,

Reference is made to our NDA #19-931 for Sulfacet® Clear Lotion (sodium sulfacetamide 10%) and to our July 1, 1994 amendment in which we corrected an error in the Chemistry, Manufacturing, and Controls section of the original application. Reference is also made to our September 21, 1994 telephone conversation with Mr. Stephan Turtil in which he indicated that some confusion had arisen regarding the formulation of the drug for the Clinical studies.

Please be informed that the same formulation of Sulfacet® Clear Lotion (sodium sulfacetamide 10%) has been used in all clinical, nonclinical, and stability studies.

As requested by Mr. Turtil, we have attached an explanation of the correction including a listing of all studies conducted and a quantitative description of the formulation of Sulfacet® Clear Lotion (sodium sulfacetamide 10%). This response is being submitted in quadruplicate to facilitate your review. In addition, a facsimile copy has been transmitted to Mr. Turtil.

We believe this submission fully responds to any outstanding comments in reference to this NDA. If you have any further comments, please contact me at (610) 454-3026.

Sincerely yours,

James R. Thompson /for

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/alh/man
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January 30, 1995

Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Gel Products
HFD-540, Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request
for Additional Copies

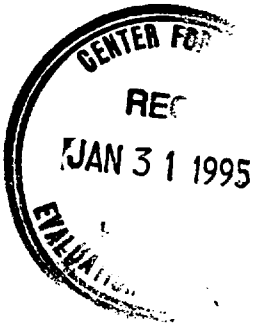
Dear Dr. Wilkin,

Reference is made to our NDA #19-931 for Sulfacet® Clear Lotion (sodium sulfacetamide 10%). Reference is also made to Dr. Janet Higgens' December 15, 1994 telephone request that we submit additional copies of the Methods Validation Package.

As discussed with Mr. Steven Turtil on January 27, 1995, we are submitting four copies of the Methods Validation Package included as Volume 1.3 of the original NDA submission of December 22, 1988. Please refer to our July 1, 1994 amendment for updated information on

In addition, I have attached a letter documenting submission of Methods Validation samples to the FDA's St. Louis office on March 20, 1991.

We have reviewed the package and believe that the original submission contains all the information required in the current Guideline for Submitting Samples and Analytical Data for Methods Validation and the informal guidance provided by Dr. Higgens in her Telephone Memorandum faxed to us on January 13, 1995.



dT 3/24/95

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[redacted]

March 10, 1995

B-

Jonathan Wilkin, M.D., Director
Center for Drug Evaluation and Research
Division of Topical Drug Products
HFD-540, Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to the recent telephone conversations representatives of Dermik (Ms. Audrey Hackman, Mr. James Thompson and Mr. Robert Klein) had with Dr. Wilson DeCamp, Supervising Chemist, and Dr. Janet Higgins, Reviewing Chemist of your staff, during which an inactive ingredient in Sulfacet® Clear Lotion with the tradename was discussed. At the conclusion of these conversations, it was agreed that the name used to identify in the Sulfacet® Clear Lotion NDA should be

As requested, this submission contains an updated List of Components and a Statement of Composition of the drug product. Please be informed that the only revisions to these sections were the renaming of

and reiterating the previous revision of the name of The actual excipients used in the Sulfacet® Clear Lotion drug product formulation have never changed.

Also included in this submission, as requested, is an infrared spectrum for

We believe this submission fully responds to all outstanding requests from the Agency regarding this application. If we can provide you with any additional information or if you have any further questions, please contact me at (610) 454-3026.

Sincerely yours,

Ronald F. Panner

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/alh/man
Enclosures

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February 21, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to our pending NDA 19-931 for Sulfacet® Clear Lotion and to Mr. Frank Cross' February 16, 1996 telephone request that we submit an electronic copy of the package insert.

As requested, a diskette containing an annotated version of the package insert in Word Perfect version 6.0 is being forwarded directly to Mr. Frank Cross under separate cover. In addition, attached please find a paper copy of this package insert, as well as the original December 22, 1988 version. Changes to the original submission have been outlined to facilitate the Agency's review.

This submission fully responds to the Agency's request. If you have any questions, please contact me at (610) 454-3026.

Sincerely,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
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February 22, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
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Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to our pending NDA 19-931 for Sulfacet® Clear Lotion and to Mr. Frank Cross and Mr. Kevin Darryl White's February 22, 1996 telephone request that we submit an electronic copy of the unannotated package insert.

As requested, a diskette containing an unannotated version of the package insert in Word Perfect version 6.0 is being forwarded directly to Mr. White under separate cover. In addition, attached please find a paper copy of this package insert.

This submission fully responds to the Agency's request. If you have any questions, please contact me at (610) 454-3026.

Sincerely,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

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Enclosures

ORIGINAL

NEW CORRESP

NC

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March 12, 1996

Jonathan K. Wilkin, M.D., Director
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Office of Drug Evaluation V
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide 10%)

Response to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to our pending NDA 19-931 for Sulfacet® Clear Lotion and to Mr. Kevin Darryl White's March 11, 1996 telephone request that we provide justification for a statement in the ADVERSE REACTIONS section of the proposed package insert.

As requested, please find attached a complete statement of the Agency's comment as well as Dermik's response.

This submission fully responds to the Agency's request. If you have any questions, please contact me at (610) 454-3026.

Sincerely,

Ronald F. Panner
Group Director
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FDA Comment:

The **ADVERSE REACTIONS** section of the Sulfacet Clear proposed package insert states, "Only one patient of 161 treated with **Sulfacet® Clear Lotion** had adverse reactions of erythema, itching and edema.". Please provide justification for the number (161) of patients.

Dermik Response:

One hundred sixty-one (161) patients represents the total number of patients treated or exposed to Sulfacet Clear Lotion in four controlled clinical efficacy trials.

Two studies (D0-1307) conducted by Dr. Swinyer and Dr. Jurnovoy were included in the original NDA submission (December 22, 1988) and contained data from 56 patients treated or exposed to Sulfacet Clear Lotion. [Please refer to Table 2, page 125, Volume 2.4 of the March 4, 1994 amendment.]

Two additional clinical efficacy trials (DL-6013-9102 and DL-6013-9302) were conducted by Dr. Parish and Drs. Maloney and Berger and were submitted in the March 4, 1994 amendment. These studies contained data from an additional 105 patients treated or exposed to Sulfacet Clear Lotion. [Please refer to Table 4, page 127, Volume 2.4 of the March 4, 1994 amendment.]

Therefore, the total number of patients treated or exposed to Sulfacet Clear Lotion in four controlled clinical efficacy trials is 161 (56 + 105).

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NEW CORRESPONDENCE

June ~~28~~ 15, 1996

Jonathan K. Wilkin, M.D., Director
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9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

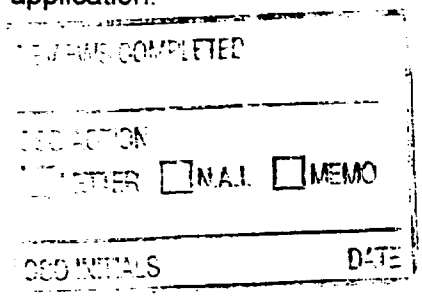
NDA 19-931
Sulfacet® Clear Lotion
(sodium sulfacetamide lotion 10%)

Notification of Intent to Amend

Dear Dr. Wilkin,

Reference is made to the above-mentioned NDA and to your June 14, 1996 letter in which you indicated that this NDA is approvable.

Therefore, in accordance with 21 CFR 314.110(a)(1), the purpose of this communication is to notify you of our intent to file an amendment to this pending application.



Sincerely,

Ronald F. Panner

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/alh/man
Encl.

DUPLICATE

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July 3, 1996

Jonathan K. Wilkin, M.D., Director
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Rockville, MD 20850

AL
NDA ORIG AMENDMENT

NDA 19-931
Klaron® Lotion 10%
(sodium sulfacetamide lotion, 10%)

Amendment to a Pending Application
- Response to Approvable Letter

Dear Dr. Wilkin,

Reference is made to your June 19, 1996 letter indicating that Dermik's NDA for Sulfacet Clear Lotion (sodium sulfacetamide lotion, 10%) is approvable and to our June 24, 1996 letter informing you that Dermik intended to amend this application and respond to your June 19, 1996 letter. This submission constitutes that response.

Included in this submission are specific responses to each of the requests made in the approvable letter . Please note that Dermik has selected a new trade name (Klaron® Lotion) for this product.

We believe this submission fully responds to all of your requests. If you have any questions regarding this submission, please contact me at (610) 454-3026.

Sincerely,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

RFP/alh/man
Encloures

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ORIGINAL
NEW CORRESP
NC

DERMIK LABORATORIES, INC.
Dedicated to Dermatology℠
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Certified Mail
Return Receipt Requested

August 23, 1996

CENTER FOR DRUG
REC'D
AUG 29 1996
FD-
AND RESEARCH

Mr. Charles Thorne
Compliance Director
U.S. Food and Drug Administration
Room 900, U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

RE: NDA 19-931
Sulfacet Clear Lotion
(sodium sulfacetamide lotion, 10 %)

Dear Mr. Thorne:

Reference is made to your November 9, 1995 correspondence in which the Agency requested additional information relative to the pre-approval inspection performed between May 1, 1995 and June 23, 1995 for Sulfacet Clear Lotion, NDA 19-931.

Specifically, the Agency has requested notification of when an amendment would be filed with the application that included an updated master formula. The Agency also requested written notification that all corrective actions have been completed for NDA 19-931.

Further reference is made to Dermik's December 11, 1995 correspondence in which Dermik stated that, in accordance with FDA's request, an amendment addressing all outstanding issues would be submitted after final review of the NDA. On June 19, 1996, Dermik received final comments on the application from the Division of Dermatologic and Dental Drug Products in which an updated master formula was requested.

Please be advised that on July 3, 1996 Dermik Laboratories, Inc. submitted an amendment to the pending application in response to the approvable letter. The updated master formula, DF 07-0066-7500-1, Revision 1b, dated July 3, 1996 was submitted as part of that amendment. A copy of the cover letter of the July 3, 1996 amendment and the updated master formula are appended with this correspondence.

Additionally, Dermik informed the Agency that a trade name of Klaron® Lotion 10% (sodium sulfacetamide lotion, 10%) has been selected for the product.

As Dermik committed to in the October 9, 1995 correspondence letter to Ms. Diana Kolaitis, District Director Philadelphia District, Dermik repeated the Preservative Effectiveness Test for Sulfacet Clear Lotion. A copy of the results for this test are enclosed for your reference.

By way of this correspondence Dermik certifies that all corrections have been completed for the NDA.

Dermik believes that all concerns with respect to the Sulfacet Clear Pre-Approval Inspection by the Philadelphia District have been fully satisfied and are sufficient to allow a recommendation of approval to the Center for Drugs.

If you have any concerns regarding this notification please contact Mr. Lane Sattler at (610) 454-2322 or the undersigned at (610) 454-8440.

Sincerely,

DERMIK LABORATORIES, INC.

Bridgette Speights

Bridgette Speights
Senior Regulatory Associate, Quality Compliance

Attachments: Cover letter of the July 3, 1996 amendment and updated master formula
Preservative Effectiveness Test Results

CC: Diana J. Kolaitis
District Director
Philadelphia District Office
U.S. Food and Drug Administration
Room 900, U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19601-2973

Johnathan K. Wilkin, M.D., Director
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

DUPLICATE

DERMIK LABORATORIES, INC.
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August 26, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

BC
NDA ORIG AMENDMENT

NDA 19-931
Klaron® Lotion 10%
(sodium sulfacetamide lotion, 10%)

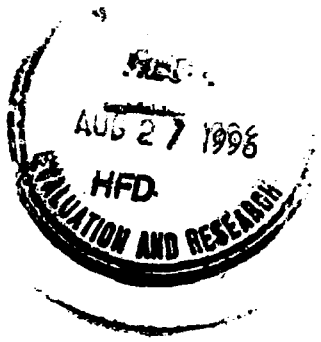
Response to FDA Request for Information

Dear Dr. Wilkin,

Reference is made to your June 19, 1996 approvable letter and to our July 3, 1996 response. Reference is also made to Mr. Kevin Darryl White's August 22, 1996 telephone request that Dermik notify the District Office of our response to the approvable letter and formally submit a copy of that letter to the NDA.

Therefore, in response to Mr. White's request, please find enclosed a copy of the August 23, 1996 letter to Mr. Charles Thorne, Compliance Director of the Philadelphia District Office.

We believe this submission fully responds to all of your requests. If you have any questions regarding this submission, please contact me at (610) 454-3026.



Sincerely,

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs
Operations

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

RFP/alh/man
Enclosures

ORIGINAL

DERMIK LABORATORIES, INC. — A RHÔNE-POULENC RORER COMPANY
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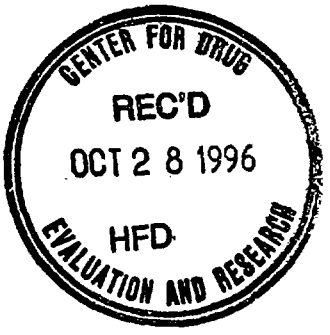
TEL. 610-454-8000

October 25, 1996

BL
NDA ORIG AMENDMENT



Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA 19-931
Klaron® Lotion 10%
(sodium sulfacetamide lotion, 10%)

Amendment to a Pending Application
- Draft Labeling

Dear Dr. Wilkin,

Reference is made to your June 19, 1996 approvable letter and to our July 3, 1996 response to that letter.

Our July 3, 1996 submission contained a revised draft package insert which incorrectly listed sodium bisulfite as an ingredient in the Description section. This submission conatins a new draft package insert which appropriately lists as an ingredient.

Please also be informed that the GMP inspection of the manufacturing site is now complete. The Philadelphia District Office has indicated that they have made a recommendation for approval of the NDA for this product.

If you have any questions regarding this submission, please contact me at (610) 454-3026.

Sincerely,

Ronald F. Panner

Ronald F. Panner
Group Director
Worldwide Regulatory Affairs

RFP/alh/man
Enclosures

REVIEWS COMPLETED
OSO ACTION:
[ ] N.A.I [ ] MEMO